

SARCOPENIC OBESITY IN SCOTISH OLDER
COMMUNITY-DWELLERS: A WEIGHT LOSS
INTERVENTION USING HIGH PROTEIN
INTAKE AND MIXED EXERCISE TRAINING TO
AUGMENT BODY COMPOSITION AND
FUNCTION IN OLDER AGE

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A PhD is like a marathon, for most of it you run on your own. At the beginning you are driven by passion for knowledge and personal ambition, and towards the end by sheer feeling of perseverance and stubbornness, clinging onto those small boosts of encouragement offered by the 'spectators' cheering you on at those very critical moments when you feel like stopping.

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Abstract

Background: Sarcopenic obesity is the condition where obesity and sarcopenia (age-related low muscle mass and strength) occur together, which may predispose older individuals to more adverse health effects than either of the two conditions alone. Thus, improvements in body composition and function are of vital importance.

Aim: The aims of this study were to A) systematically search the databases for nutritional and/or exercise interventions in sarcopenic obesity and assess their effectiveness in augmenting body composition and function. B) Screen Scottish older community-dwellers for sarcopenia and obesity. C) Implement a nutritional and exercise programme for individuals with sarcopenic obesity.

Methods: A) Four databases were systematically searched for trials with sarcopenic obese older adults. B) Scottish community dwellers (≥ 65 years) were screened for body fat (using bioelectrical impedance analysis; BIA), body mass index (BMI), muscle mass, and grip strength. C) Those with a high % body fat (≥ 28 % in men; ≥ 40 % in women) and low skeletal muscle mass index (≤ 10.75 kg·m⁻² in men; ≤ 6.75 kg·m⁻² in women) were randomly allocated to a 16-week intervention with exercise (EX) or exercise plus dietary modifications (EXD). The EX group followed a mixed-exercise training programme, whereas the EXD followed the same exercise protocol alongside an energy-deficit (500 kcal daily deficit) and high protein diet (1.2 – 1.5 g kg bodyweight⁻¹).

Results: A) Two studies were identified from the literature with sarcopenic obese participants (one diet and one resistance-exercise trial) but neither noted a significant change in body composition. However, resistance exercise training significantly improved physical function. B) In total, 108 (men, n=29; women, n=79) adults (median (IQR) age, 70 (67, 75) yr) took part in the screening test. Prevalence of sarcopenia was 14.8%, of obesity 27.8 % (using BMI) vs 63.0 % (using BIA), and sarcopenic obesity 4.6 % (using BMI) vs 12.0 % (using BIA). C) After 16 weeks of the intervention, the median (IQR) changes in EXD vs EX in bodyweight, fat mass and muscle mass were: -5.0 (-5.0, -6.8) kg vs. +0.5 (0.0, 1.0) kg, -4.7 (-4.8, -4.2) kg vs 0.0 (-0.4, 0.7) kg, and +0.1 (-0.4, 0.7) kg vs +0.5 (0.3, 0.7) kg, respectively. Improvements that may be of clinical significance were noted in both groups for strength and physical function.

Conclusion: More intervention trials are needed with sarcopenic obese older adults. Prevalence of high adiposity in Scottish older adults may be higher than what has been previously documented. High adiposity and the use of BMI may mask sarcopenia and sarcopenic obesity. A high-protein energy-restriction diet with exercise training can potentially improve body composition, and augment physical function in older adults with low muscle and high fat mass.

Keywords: sarcopenia, obesity, sarcopenic obesity, body composition, older age, weight loss, high protein diet, exercise training, physical function

Abbreviations

% BF, Percent body fat

1RM, 1 repetition maximum

25(OH)D, 25-hydroxycholecalciferol

ACSM, American College of Sports Medicine

ALM, Appendicular lean mass

ALP, Alkaline Phosphatase

ASM, Appendicular skeletal mass

ASMI, Appendicular skeletal muscle index

AUC, Area under the curve

BHFNC, British Heart Foundation National Centre

BIA, Bioelectrical impedance analysis

BMI, Body mass index

BP, Blood pressure

BSAP, Bone specific alkaline phosphatase

BW, Bodyweight

CHD, Coronary heart disease

CHO, Carbohydrates

CRP, C-reactive protein

CT, Computed tomography

CVD, Cardiovascular disease

DXA, Dual-Energy X-ray Absorptiometry

DBP, Diastolic blood pressure

EAA, Essential amino acid

EB, Elastic band

EER, Estimated energy requirements

EI, Energy intake

EMS, Electromyostimulation

ER, Energy restriction

EWGSOP, European Working Group in Sarcopenia in Older people

FFM, Fat free mass

FM, Fat mass

GH, Growth hormone

GLUT-4, Glucose Transporter type 4

GP, General practitioner

GS, Gait speed

HR, Heart rate

HsCRP, high-sensitivity C-Reactive protein

HSC, High-speed circuit

Ht, Height

IADL, Instrumental activities of daily living

IBS, Irritable bowel syndrome

ICC, Intra-class correlation coefficient

IGF-1, Insulin-like growth factor -1

IL-1, Interleukin 1

IL-6, Interleukin 6

IL-10, Interleukin 10

LM, Lean mass

MCID, Minimal clinically important difference

MDC, Minimal detectable change

MoCA, Montreal cognitive assessment

MPB, Muscle protein breakdown

MPS, Muscle protein synthesis

MRI, Magnetic resonance imaging

mTOR, Mechanistic target of rapamycin

NDNS, National diet and nutrition survey

NHSGGC, NHS Greater Glasgow and Clyde

NICE, National Institute for Health and Care Excellence

PEF, Peak expiratory flow

QMU, Queen Margaret University

RCS, Repeated chair stands

RCT, Randomised control trial

RE, Resistance exercise

SAD, Sagittal abdominal diameter

SACN, Scientific advisory committee for nutrition

SBP, Systolic blood pressure

SD, Standard deviation

SE, Standard error

SEE, Standard error of the estimate

SEM, Standard error of the mean

SMI, Skeletal muscle index

SMM, Skeletal muscle mass

SPPB, Short physical performance battery

TBM, Total body mass

TEI, Total energy intake

TNF α , Tumour necrosis factor alpha

TSE, Task-specific exercise

TSH, Thyroid stimulating hormone

TUG, Timed up-and-go

WC, Waist circumference

WHO, World Health Organisation

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'The most famous doctors cure by changing the diet and lifestyle of their patient and, by using other substances. Such capable doctors have the knowledge and ability to use the therapeutic properties of most natural or man-made products'
The Art 2.6

'Those who are constitutionally very fat are more apt to die quickly than those who are thin'
Aphorisms 2.44

Hippocrates

(Jones 1923; Tsiompanou and Marketos 2013)

'The doctor of the future will give no medicine, but will instruct his patient in the care of the human frame, in diet and in the cause and prevention of disease'

Thomas Edison

(Anda et al. 1987)

Introduction

Although the previous quotes are separated by approximately 2,000 years, they acknowledge both the importance of healthy body composition and how the doctors should embrace lifestyle changes as preventative therapy, without however, denying new medical knowledge or the advancements that may come with it. Although the medical advancements over the past decades have been ground-breaking, one could argue that the essence of the words by Hippocrates and Edison, has not been fully materialized. A criticism of contemporary medicine is that it perhaps focuses more on alleviating symptoms, mostly by the use of pharmaceutical and surgical interventions, rather than embracing a person-centred approach focusing on lifestyle factors, such as diet and physical activity (Tsiompanou and Marketos 2013).

Medical advancements have led to a global increase in life expectancy and consequently in the number of older adults (Nikolich-Zugich et al. 2016). However, this demographic shift is not always translated into more healthy years, since it is accompanied by an increase in rates of disabling and often fatal chronic conditions (Group Advisory Council on Ageing Society 2012). Approximately 14% of adults aged 65-75 years and 45% of the over 85s require help for activities of daily living (Dreyer and Volpi 2005), while falls are the leading cause of accidental-injury deaths in older adults in the UK (including Scotland) and the US (CDC 2011; ONS 2015; NRS 2015). In addition, 70% of hospital admissions and 70% of NHS costs can be accounted for by older patients with a long-term condition such as osteoporosis (NOS 2011). Hip fractures amongst older adults in the UK account for 85,000 hospital admissions, which equates to £1.9 billion in financial costs for the NHS per year (NOS 2011). Moreover, cardiovascular disease remains one of the biggest mortality risk factors for men and women aged 65-79 years old (ONS 2015).

Similarly in the US, patients older than 65 years account for 50% of healthcare costs, with the leading cause of admissions being cardiovascular disease (Spector et al. 2012). It is therefore apparent that the aim of geriatricians and public health systems is not only to cease the rising prevalence of disability, morbidity and mortality at a population level but also to extend the years of healthy life at an individual level (Nikolich-Žugich et al. 2016).

Sarcopenic obesity is the progressive loss of muscle mass and function with a concomitant increase in body fat that comes with advancing age (Baumgartner 2000). It is also one of the key metabolic and physiological processes increasing the risk of frailty, bone fractures and disability, as well as non-communicable diseases such as cardiovascular disease (CVD), metabolic syndrome and type II diabetes (Gusmao-Sena et al. 2016; Molino et al. 2016). In addition, there is evidence suggesting that sarcopenic obesity can make older individuals more susceptible to physical disability compared to sarcopenia or obesity alone (Baumgartner 2000).

Two of the most fundamental and modifiable lifestyle parameters that can attenuate the deleterious effects of ageing on body composition, and augment muscle mass and function as well as mobilization of adipose tissue, even in advancing age, are diet and exercise (Witard et al. 2016a). The scientific community has placed emphasis on caloric restriction (Picca et al. 2017) with a particular focus on optimal protein intakes, and exercise training usually with a combination of resistance and aerobic exercises (Churchward-Venne et al. 2014; Witard et al. 2016a).

In the following chapter, the definition, aetiology, prevalence, and health consequences of sarcopenic obesity will be presented, followed by management strategies based predominantly on nutritional and exercise regimes that have shown potential in augmenting body composition and function in older age. At the end of *Chapter 1*, the aims and objectives of this PhD thesis are presented.

Chapter 1. Literature review: Sarcopenic obesity in ageing

1.1 Overview

The ageing process can affect the human body in several ways via complex pathways. Considering that more than 90% of the older adults (>65 years) suffer from one or more chronic conditions (Hung et al. 2011), it is challenging and possibly unrealistic to isolate and study the trajectory of single compartments of the body such as the muscle or adipose tissue without investigating whole body homeostasis. Moreover, different stressors (genetic or environmental) can potentially modify the trajectory of metabolic processes, and affect the quantity as well as the quality of tissues, such as the ageing muscle. Therefore, where possible the mechanisms leading to sarcopenic obesity will be acknowledged, however greatest emphasis will be placed on the outcomes of muscle atrophy and increased adiposity in relation to comorbidities, physical function and health related quality of life. Thus, it will be discussed how sarcopenic obesity can potentially lead to functional impairments, poor clinical prognosis, increased risk of bone fractures, CVD and metabolic syndrome, and consequently loss of independence/ institutionalisation, lower quality of life, and increased morbidity and mortality rates. Moreover, it will be discussed how physical inactivity and poor dietary habits can affect the onset/progression of sarcopenic obesity.

1.1.1 Definition and operational diagnosis of sarcopenia, obesity and sarcopenic obesity

One of the most noticeable changes in older age is the loss of muscle, accompanied by a decline in strength and physical function. The peak in muscle mass and strength is usually reached between 25 and 30 years of age and after that it declines (Lexell et al. 1988). After the third decade of life muscle mass declines at a rate of 0.5-2% per year, whereas the loss of strength is more precipitous with a decline of 3-4% expected annually (Mitchell et al. 2012). Therefore, by the age

of 80 approximately 40% of the muscle mass may be lost (Lexell et al. 1988). The term ‘sarcopenia’, was initially introduced to define the age-related atrophy of muscle mass (Evans 1995; Rosenberg 1997). Rosenberg noted that the most significant change that comes with age is the loss of lean mass, which is primarily driven by the loss of muscle tissue. The importance of this condition was explicitly expressed by Rosenberg: ‘*no decline with age is as dramatic as the decline in lean body mass*’ (Rosenberg 1997). According to Rosenberg, the loss of lean mass that occurs with increasing age can have a deleterious effect on energy intake and nutritional status, mobility, breathing and independence. He also suggested that in order for this phenomenon to be acknowledged as a serious condition by the scientific community, it should be given a name; therefore, he suggested two terms, sarcomalacia and sarcopenia. The latter prevailed in the literature in the following years (Rosenberg 1997).

Baumgartner et al. (1998) provided one of the first operational definitions of sarcopenia which, similar to osteoporosis, was based on muscle mass two standard deviations (SDs) below the appendicular muscle mass (corrected for height) of a young and healthy population cohort. Baumgartner reported a prediction equation for appendicular skeletal mass (ASM) based on regression analysis derived from Dual-Energy X-ray Absorptiometry (DXA) body composition analysis of 301 older men (77.2 ± 5.8 yr) and women (76.4 ± 6.7 yr). Values for weight, height, hip circumference, grip strength and sex were required for the estimation of ASM. Subsequently, the ASM of 808 older white Hispanic and Non-Hispanic men and women was estimated (using the prediction formula) and was divided by squared height to produce the appendicular skeletal muscle index (ASMI). It was evaluated that adjusting for height² was the most reliable way of eliminating differences in muscle related to greater height, regardless of age, gender and ethnicity. The ASMIs derived from the older cohort were then compared against the cut-offs for sarcopenia that were

derived from a healthy young cohort (n=229 non-Hispanic men and women, 18-40 yr) who had undergone body composition measurements by Dual-Energy X-ray Absorptiometry (DXA).

Although sarcopenia is still frequently regarded as the loss of muscle mass in the literature (Manini and Clark 2012; Morley 2012; Maltais et al. 2016), more often than not the term has been used to represent the age-related loss of muscle mass that is accompanied by poor strength or poor physical function (Cruz- Jentoft et al. 2010). Low strength alone has also been termed ‘dynapenia’ in order to distinguish it from low muscle mass (Manini and Clark 2012). To date, several definitions and cut-offs for sarcopenia have been proposed, the most popular of which include an index of muscle mass, usually two SDs lower than the respective index of a young cohort corrected for height, gender and ethnicity, along with a cut off for low physical function (usually low gait speed) and/or strength (Cruz- Jentoft et al. 2010; Muscaritoli et al. 2010; Fielding et al. 2011; Morley et al. 2011). More information about these studies is presented in **Table 1.1**, alongside their strengths and limitations.

In addition to potential overlaps or discrepancies between the cut-offs, the fact that these definitions have been introduced in the current decade explains why their validity to predict health outcomes (e.g. disability, non-communicable diseases, morbidity and mortality) in the long term is yet to be determined. Nevertheless, based on preliminary evidence, the definition proposed by the European Working Group in Sarcopenia in Older people (EWGSOP) (Cruz-Jentoft et al. 2010) has been reported to have higher validity compared with the others, for predicting the incidence of falls (Bischoff-Ferrari et al. 2015). In that study 445 older adults were diagnosed with sarcopenia based on all current definitions and were followed-up for three years to allow for the

calculation of incidence of falls. Interestingly, the authors also tested the performance of definitions based on low muscle mass alone (using the criteria set by Baumgartner et al. (1998), which showed consistent validity in predicting the rate of falls. In fact the validity of the criteria by Baumgartner and colleagues to predict incidences of falls was similar to the ones that incorporated criteria of both muscle and strength/function, such as the one from the EWGSOP) (Bischoff-Ferrari et al. 2015).

Table 1.1 Definitions of age-related sarcopenia and diagnostic criteria

Aim/ Group	Definition of age-related sarcopenia	Diagnostic Criteria	Population Group	Strengths + Limitations -
Consensus definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al. 2010)	Low muscle mass combined with either a) low strength or b) low performance	<p><u>Muscle</u>: 2SDs below the reference values for healthy young adults. Assessed by: $ASM \cdot ht^{-2}$ or $SMM \cdot ht^{-2}$ or the residuals method (as explained by Newman et al. 2003a)</p> <p><u>Low Strength</u>: assessed by HG, knee flexion/extension, PEF</p> <p><u>Low performance</u>: $SPPB \leq 8$, low gait speed, stair climb power test, TUG test</p>	Population data from several studies (e.g. Baumgartner et al. 1998; Newman et al. 2003a, Janssen et al. 2002)	<p>+ Allows for flexibility in operational diagnosis, with a variety of option for methodologies and appropriate cut-offs</p> <p>-Different cut-offs and assessment protocols make comparisons between studies difficult</p>
Consensus definition of sarcopenia by the International Working Group on Sarcopenia (IWGS) (Fielding et al. 2011)	Loss of skeletal muscle mass and function	<p><u>Muscle</u> < 20 percentile of indices for healthy older adults, or $< 7.23 \text{ kg} \cdot \text{m}^{-2}$ (men) $< 5.67 \text{ kg} \cdot \text{m}^{-2}$ (women). Assessed by $ALM \cdot ht^{-2}$;</p> <p><u>Function</u>: $GS < 1 \text{ m} \cdot \text{s}^{-1}$ (if ambulatory)</p>	Health ABC population; 2,984 Caucasian and African American men and women 70-79 years old (Newman et al. 2003a)	<p>+Fixed values</p> <p>-Requires specific equipment to measure ALM; may not be applicable to all ethnic groups</p>
Consensus definition of sarcopenia with limited mobility by the Society of Sarcopenia, Cachexia and Wasting Disorders (Morley et al. 2011)	Low muscle mass with low walking speed	<p><u>Muscle</u>: $ALM \cdot ht^{-2} < 2$ SDs of healthy adults (20-30 years old)</p> <p><u>Walking speed</u>: $GS \leq 1 \text{ m} \cdot \text{s}^{-1}$ or walk $< 400\text{m}$ in 6 min.</p>	NHANES IV population; 2,402 men and women from three US ethnic groups: Non-Hispanic Whites, Non-Hispanic Blacks, and Mexican Americans, 20-30 years old (Kelly et al. 2009)	<p>+Clear definition; Using a young population of the same ethnic background makes the results more valid for the given population</p> <p>-Requires a young and healthy population group of the same ethnic</p>

				background; Requires specific equipment to measure ALM
Consensus definition of sarcopenia by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics” (Muscaritoli et al. 2010)	Loss of muscle mass and muscle strength/function Low gait speed, e.g. a walking speed below 0.8 m/s in the 4-m walking test	<u>Muscle</u> : SMI: $\text{SMM} / \text{Body Mass} \cdot 100$; \geq Class I sarcopenia: SMI within one to two 2SDs below the mean SMI of a young cohort. Class 2 sarcopenia: $\text{SMI} \geq 2\text{SD}$ below the mean SMI of a young cohort. <u>Function</u> : $\text{GS} < 0.8 \text{m} \cdot \text{s}^{-1}$ in the 4-m walk test OR by one ‘ <i>of the well-established functional tests utilized locally</i> ’	NHANES III population: 3,298 women and 3,116 men, non-Hispanic white, non-Hispanic black, and Mexican American (Janssen et al. 2002)	+Body composition assessment can be done with BIA; accounts for body mass -Does not account for stature; may not be applicable to all ethnic groups

Notes: ALM, appendicular lean mass; ASM, appendicular skeletal muscle; BIA, Bioelectrical impedance analysis; FFM, fat free mass; GS, gait speed; ht, height; PEF, peak expiratory flow; SD, standard deviation; SMM, skeletal muscle mass; SPPB, Short Physical Performance Battery Test, TBM, total body mass; TUG, timed up-and-go.

In addition to sarcopenia, another important health risk factor in older age is frailty. It is important to note that sarcopenia and frailty are two different entities. Frailty is the clinical condition in which at least three of the following criteria are present: muscle weakness (low strength), low endurance (self-reported exhaustion), slow gait speed, unintentional weight loss and low physical activity (Fried et al. 2001). Both sarcopenia and frailty are highly prevalent in the older populations and are associated with adverse health events (Baumgartner et al. 1998; Fried et al. 2001); however, a clear framework within which these two conditions can be explored and studied is currently lacking (Cesari et al. 2014). According to Cesari and colleagues although in theory sarcopenia and frailty have fairly distinct theoretical definitions, there is a lack of a unique operational definition. The issue may originate in the catabolic nature of these two conditions that gives rise to many, and often overlapping manifestations, the most important of which is weakness and physical disability. Therefore, the question is often whether frailty is the result of sarcopenia or vice versa.

Another condition that is often met in older age is the gradual gain of fat mass that accumulates in the body's adipose stores and especially around the trunk and the visceral depots (Racette et al. 2006). It has been well documented that fat accumulation around the central region continues across the lifespan from middle age to older age, with the waist circumference increasing by approximately $0.7 \text{ cm}\cdot\text{year}^{-1}$ (Noppa et al. 1980). Furthermore, intermuscular adipose tissue accumulation (or infiltration) increases with age (Goodpaster et al. 2001). Due to this gradual redistribution of fat, and change in body composition, older adults may have more visceral fat compared to their middle-age counterparts even at substantially lower bodyweights (Borkan et al. 1985). Although at tissue level the accumulation of fat *per se* does not necessarily elicit a reduced capacity for maximal oxygen uptake, it may limit the capacity to exercise due to the increased

effort that is required to move the excess mass through space (e.g. when walking, running or performing body weight exercises) (Carrick-Ranson et al. 2012). The fat infiltrating the muscle tissue can also change the physiological properties of the muscle, resulting in reduced muscle quality (force production per unit of muscle) (Visser et al. 2005).

Therefore, obesity is a condition characterised by an unhealthy excess of adipose tissue (Villareal et al. 2005). The most commonly used criterion to classify obesity is total body mass corrected for height, also known as body mass index ($BMI = \text{total body mass} \cdot \text{height}^{-2}$), with a cut-off for obesity at 30 kg m^{-2} (World Health Organisation 2017). Currently, this cut-off is age and gender-independent but ethnicity dependent, with Asians exhibiting overweight and obesity-associated risks at BMIs as low as $22\text{-}25 \text{ kg m}^{-2}$ (World Health Organisation 2017). Although BMI is perhaps the easiest and most practical test to perform, it may not be appropriate for use in older adults as it cannot account for body composition changes that come with ageing, thus its usefulness has been questioned (Villareal et al. 2005). The age-related body composition changes and the appropriateness of using BMI in older adults to identify high body fatness is discussed more thoroughly in the next section (1.1.4) in the context of health consequences of obesity and especially when it parallels, or more precisely masks, sarcopenia in older age.

The need for a more reliable method for the identification of high adiposity has prompted the use of more direct measurements of body fat mass, which is usually expressed as a percentage in relation to total body mass, termed percent body fat (%BF) (with cut-off values usually ranging $27\text{-}30\%$ and $35\text{-}40\%$ in older men and women, respectively (Donini et al. 2014)). This method requires the assessment of body fat by Dual-energy X-ray absorptiometry (DXA), magnetic

resonance imaging (MRI), bioelectrical impedance analysis (BIA), computed tomography (CT) or air-displacement plethysmography (ADP). Other indices to classify obesity have been increased waist circumference (individually or combined with BMI) and more rarely the mid-arm fat area and visceral fat area (Donini et al. 2014; Poggiogalle et al. 2014).

Sarcopenic obesity is characterised by the co-occurrence of sarcopenia and obesity, i.e. high fat mass and low muscle mass. Heber et al. (1996) first defined the term sarcopenic obesity as low lean mass, out of proportion to fat mass. Since there are many diagnostic criteria for sarcopenia and obesity but not a single universally accepted definition for each, it is not surprising that many different criteria exist for the sarcopenic obese phenotype. Typically a combination of one criterion for sarcopenia (e.g. low muscle mass with or without low strength) is used along with an obesity criterion (e.g. high %BF or high BMI) to identify sarcopenic obesity (Donini et al. 2014; Poggiogalle et al. 2014). In other cases, new diagnostic criteria with sarcopenic obesity-specific cut-offs have been developed e.g. ratios of adiposity to muscle, total fat mass to lower-limb muscle mass, body weight to fat free mass (FFM), and total fat mass to FFM (Auyeung et al. 2012). As mentioned previously, the ability of the operational definitions to predict future health incidences has not been assessed either for sarcopenia or sarcopenic obesity, therefore the scientists usually adopt criteria that are compatible with the available resources, the research conditions or questions that need to be addressed; usually, MRI or DXA are preferred in clinical settings and/or in studies where greater financial resources and trained personnel are available, whereas BIA and anthropometry are used primarily in field studies, where the simplicity of measurements and a high level of practicality is of primary importance.

1.1.2 Aetiology of sarcopenic obesity in older age

The main cause of ageing is a time-dependent accumulation of damage at a molecular and cellular level (López-Otín et al. 2013). The underpinning mechanisms (or ‘hallmarks of ageing’) may explain the ageing trajectory (including the sarcopenic obese phenotype), and involve DNA damage, loss of proteostasis (failure of autophagy to control damaged proteins), dysregulated nutrient sensing (that is, the dysregulation of pathways involved in glucose and amino acid metabolism, low energy or high energy states sensing, such as insulin, insulin-like growth factor (IGF), mechanistic target of rapamycin (mTOR), adenosine monophosphate-activated protein kinase (AMPK) and sirtuins), mitochondrial dysfunction, cellular senescence, stem cell exhaustion and deregulated intercellular communication (extensively reviewed by López-Otín et al. 2013). Although these ‘hallmarks’ provide the fundamental basis of the age-related changes, ultimately, the direction of muscle gain or loss is dictated by the difference in rates of muscle protein synthesis (MPS) and muscle protein breakdown (MPB) (**Figure 1.1**), that is, the net protein balance. However, in older age, the sensitivity of pathways that lead to muscle protein synthesis (i.e. muscle growth) in response to anabolic stimuli (e.g. food and exercise) is reduced, a phenomenon termed ‘anabolic resistance’ (Burd et al. 2013).

The underlying mechanisms for the age-related anabolic resistance may include a decline in anabolic signalling, impaired protein digestion and absorption, reduced aminoacidemia due to increased splanchnic retention, impaired muscle perfusion and lower skeletal muscle uptake of amino acids (Burd et al. 2013; McLeod et al. 2016). Moreover, there is a decrease in the number of alpha-motorneurons, type II muscle fibres’ number and size, type II satellite cells (muscle stem cells), as well as a decline in the capillarisation of muscle fibres (Guccione et al. 2012; Snijders and Parise 2017). Further, in older adults the distance between muscle fibres and nearest capillaries

is greater than in their younger counterparts, which leads to a diminished delivery of anabolic agents and may explain to some extent the blunted muscle satellite cell response (concept termed ‘capillary impact zone’) (Snijders and Parise 2017). Since muscle fibres are post-mitotic they rely on the presence of functional satellite cells for regeneration and long-term hypertrophy (García-Prat et al. 2016). Satellite cells can maintain a quiescent state through autophagy, which degrades and removes misfolded proteins and organelles, such as mitochondria (García-Prat et al. 2016). However, in older age the autophagic system is impaired, leading to an accumulation of damaged proteins and eventually resulting in stem cell exhaustion (senescent state) (García-Prat et al. 2016). Thus, it is easily understood that the factors leading to sarcopenia and/or obesity are intrinsically complex and multifactorial, and in fact, have not been yet fully elucidated (Molino et al. 2016).

An in-depth discussion of the metabolic pathways involved in molecular, cellular and tissue level is not directly involved in the scope of this thesis. Instead, emphasis will be placed on the physiological manifestations of these pathways and the aetiology of sarcopenic obesity focusing on lifestyle choices and how these can potentially affect the development of the sarcopenic obese phenotype. For example, neurodegeneration, inflammation, reduced delivery of amino acids to the muscle, as well as the age-related decline in anabolic hormones may be the outcomes of the cellular and molecular ‘hallmarks’ mentioned above. However, their manifestations i.e. reduced function and neuromuscular coordination, loss of muscle and/or gain of fat, can affect (and equally be affected by) the development of sarcopenic obesity as well as by lifestyle choices such as diet and physical activity (Morley 2012). In this regard, the most important factors that may affect the development/progress of sarcopenia and obesity are malnutrition, physical inactivity, neurodegeneration and inflammation, along with age-related declines in anabolic hormones.

Therefore, any intervention programme aiming to improve muscle mass and function while inhibiting muscle breakdown and accumulation of fat tissue should address most of these factors.

Anorexia of ageing and energy-protein malnutrition

Although basal, postabsorptive MPS rates between young and older adults are similar (Volpi et al. 2001), the feeding-induced MPS response in older adults is blunted compared with young adults, and this is even more pronounced in older obese sedentary adults (Phillips 2014; Smeuninx et al. 2017). While resistance exercise can elevate MPS even in older age, it is not likely to restore a ‘youthful response’ to feeding-induced MPS (Villareal et al. 2011; Phillips et al. 2014). However, it has been recently suggested that the old muscle can have a similar MPS potential with the young muscle, if older adults consume ~2-fold higher amounts of protein per meal in order to overcome the anabolic resistance (Yang et al. 2012; Moore et al. 2015). In these studies graded dose-response trials showed that older adults need ~40 g whey protein after exercise to reach a plateau of MPS, whereas their younger counterparts reached a maximal plateau after ingestion of ~20 g protein. In terms of protein intakes in a single meal relative to bodyweight, Moore et al. (2015) noted that a maximal MPS rate can be achieved with ~67% higher doses in older vs young adults (0.40 g protein kg bw⁻¹ meal⁻¹ vs 0.24 g protein kg bw⁻¹ meal⁻¹, respectively). These studies will be further discussed throughout the thesis, but it is important to acknowledge here that although the response to anabolic stimuli may be blunted in older age, it is not impossible to achieve a ‘youthful response’.

In advancing age, a reduced or sub-optimal MPS is ultimately the main driver of decline in muscle tissue accretion, although in cases of inactivity a transient increase in muscle protein breakdown

is also possible (Wall and van Loon 2013). Therefore, an adequate provision of energy and nutrients (e.g. protein, essential amino acids (EAAs) and particularly leucine) is essential in order to stimulate, as well as provide the substrates for the muscle protein synthetic response in older age (Witard et al. 2016a). However, the issue in older age becomes more complex considering that older adults may limit the amount of food and protein consumed due to anorexia of ageing or malnutrition, which may influence muscle growth processes (Morley 2012). Moreover, there are age-related changes in appetite and neurosensory capacity that either discourage older individuals from eating, or change their food preferences in favour of sugar-rich foods e.g. confectionary (Toffanello et al. 2010). Therefore, it is possible that a below-optimal protein intake may co-exist with a normal or even high energy intake. Overfeeding and overconsumption of energy dense foods can also reflect a state of malnutrition which can lead to obesity and increased inflammation, especially when combined with physical inactivity (Roubenoff 2006), but in this instance the term malnutrition is used to describe the protein-energy wasting (Biolo et al. 2014).

Food insecurity, defined as the limited availability, access to or ability to purchase safe food is a major concern for older adults, since approximately one out of four Scottish ‘households below average income’ is a household with one or more individuals ≥ 65 years old (Douglas et al. 2015). In the UK in general, one out of seven pensioners lives in poverty and approximately 1.3 million older adults are at risk of, or already suffering from malnutrition, the vast majority of which are community-dwellers (Elia and Smith 2009; Age UK 2014). Furthermore, upon admission to a UK hospital one out of three older individuals are at risk of malnutrition (Malnutrition Task Force 2014).

Potential cases of malnutrition (poor energy-protein status) can be identified with the use of a screening tool (e.g. the Simplified Nutritional Assessment Questionnaire (SNAQ; Wilson et al. 2005) the Mini Nutritional Assessment tool (MNA; Guigoz et al. 1994) or the Malnutrition Universal Screening Tool (MUST; Elia 2003) and following that, diagnosed by involuntary weight loss, low BMI and low lean mass index (Sánchez-Rodríguez et al. 2016). In a study with adults aged ≥ 70 years admitted to a hospital geriatric ward with a non-disabling disease (and ambulatory prior to hospitalisation), the rates of malnutrition and sarcopenia were assessed (Sánchez-Rodríguez et al. 2016). Approximately 20% of the patients were found to be malnourished and almost 83% of them were sarcopenic, whereas in the non-malnourished cohort the prevalence of sarcopenia was almost half (45%). This finding is important considering that older patients with hip fractures have often been reported to be malnourished (Huang et al. 1996; Hoekstra et al. 2011) and further, to consume low amounts of protein pre- and post-operatively ($\sim 48 \text{ g} \cdot \text{day}^{-1}$), and especially of animal origin (Munger et al. 1999; Hoekstra et al. 2011).

Apart from anorexia, food insecurity, poverty and hospitalisation, depression is another important factor affecting food intake in older age in both institutionalised and community-dwelling older adults (Cabrera et al. 2007; Thakur and Blazer 2008). Also, polypharmacy, dysphagia, malabsorption and/or maldigestion can result in reduced energy intakes (Slaughter et al. 2011), and potentially in sarcopenia since low energy and protein intakes may lead to muscle losses in the physically active (Pasiakos et al. 2010), as well as inactive older adults (Biolo et al. 2007). Therefore, regardless of physical activity levels, protein-energy malnutrition can negatively affect the responsiveness of skeletal muscle to intervention. On the other hand physical inactivity can also result in reduced muscle mass and function regardless of the availability of nutrients/protein (Dirks et al. 2017).

Physical Inactivity

Physical inactivity can lead to decreased muscle fibre size due to decreased mechanical stimuli, which is an anabolic factor for the muscle fibres (Narici and Mafulli 2010). The muscle disuse during periods of intentional or unintentional inactivity (e.g. leg-cast, hospitalisation, bed-rest) can significantly reduce MPS rates even in young adults (Glover et al. 2008). In older adults two weeks of leg immobilisation can reduce muscle size by 5%, whereas retraining is not likely to restore muscle size to its pre-inactivity levels (in contrary to the young muscle which retains this ability) (Suetta et al. 2009). Even in the absence of complete immobilisation, a 76% reduction in daily step-count can decrease lean mass by 3.9% ($p < 0.001$) in as little as two weeks in healthy older adults ($n=10$, age = 72 ± 1 yr) (Breen et al. 2013). In addition to reduced muscle mass, the step reduction significantly lowered post-absorptive insulin sensitivity and MPS, and mediated an increased inflammatory response (as indicated by increased levels of Tumor Necrosis Factor α (TNF α) and C-Reactive protein (CRP)), as well as post-prandial insulin resistance. In fact, in cases of older adults exposed to complete inactivity (e.g. bed-bound), impaired insulin action and dysregulation of glucose metabolism has been observed within five days or even less, possibly mediated by an increased inflammatory response and imbalances between energy intake and expenditure (Stephens et al. 2010; Kwon et al. 2015a).

This loss of muscle mass can further prevent older adults from participating in physical activities due to the increased feeling of tiredness and muscle weakness, and thus continue fuelling the cycle of inactivity-inflammation-muscle atrophy (Roubenoff 2006). Another outcome of the inactivity-induced muscle atrophy is a lower resting metabolic rate. It has been postulated that a 6% reduction

in basal metabolic rate (or 30-40 kcal·day⁻¹) is to be expected for every kilogram of lean mass lost during bed-rest inactivity (Ritz et al. 1998; Biolo et al. 2014). The lower resting metabolic rate, combined with a lower energy expenditure due to inactivity can predispose older adults to positive energy balance that can consequently lead to gains in fat mass (Roubenoff 2006). Additionally, this effect is even more pronounced in older adults, due to other contributing factors and comorbidities (e.g. inflammation, insulin resistance, age-related sarcopenia) (Biolo et al. 2014). Therefore, the reduction of muscle size and gain of fat along with the increased perception of effort can further exacerbate the perception of fatigue and prevent older adults from participating in physical activities, fuelling the vicious cycle of inactivity and impaired muscle mass/function.

Neuromuscular changes

One of the mechanisms contributing to the loss of muscular strength and function is the loss of motor units, a process also known as denervation of muscle fibres (Guccione et al. 2012). A motor unit consists of an alpha-motoneuron that innervates and activates all the muscle fibres that are connected to it. Advanced ageing has been associated with a 50% loss of available alpha-motorneurons (Lexell 1995). The denervated muscle fibres then join neighbouring and active motor units, which in turn results in bigger motor units (Guccione et al. 2012). The lower efficacy of the bigger motor units combined with the fact that the denervation is more likely to happen in type II (fast-twitch) muscle fibres than in type I (slow-twitch) accounts to some extent for the impaired coordination, tremor, fatigue and loss of speed and power which are often experienced by older adults (Lexell 1995; Roubenoff 2000; van Beveren 2012).

Alongside the denervation of muscle fibres, there is a concomitant reduction in the number of both types (I and II) of muscle fibres with age (Lexell et al. 1988). Although the percentage of type I and type II fibres may remain the same with increasing age, the type I fibres occupy more muscle area due to the atrophy (reduction in size by 13-31%) of type IIa and IIb fibres (Coggan et al. 1992). This reduction is more pronounced in type II fibres possibly due to the increased degradation of type II myogenic satellite cells and therefore, there is a lower capacity for regeneration and growth of the fast-twitch muscle fibres (Verdijk et al. 2006).

As a result, a decline in muscular strength and power with time has been observed. Namely, handgrip strength and knee extension strength have been documented to decline at a rate of 1.5-2.0% p.a., whereas the decline in power can be more precipitous, at rates of 3.2-3.7% p.a. (Skelton et al. 1994). This decline in power has been found to correlate strongly with functional tests such as the ‘chair rise’ in healthy older adults ≥ 65 years (Skelton et al. 1994), as well as in old institutionalised adults with multiple conditions (Bassey et al. 1992). Interestingly, these studies have also documented that handgrip strength correlates with leg power (Skelton 1994), and the ‘chair rise’ test with gait speed (Bassey et al. 1992). In general, both maximal force production and explosive force production are important for physical function in older age (Granacher et al. 2008). For example, in order to maintain postural control after an external disturbance of balance a rapid generation of force is necessary in order to counteract these disturbances and regain stability (Orr 2010). Older adults who have experienced falls are likely to produce ~ 24% less lower body power compared to their ‘non-faller’ counterparts (Skelton et al. 2002). Moreover, muscular weakness is also associated with mobility limitations and falling (Skelton et al. 2002), as is polypharmacy, lack of physical activity, and reduced capacity for physical movements, e.g. inability to bend over (O’Loughlin et al. 1993; Skelton et al. 2002). Consequently, the result of the

denervation and atrophy of type II fibres can negatively affect all daily activities that require a certain capacity for force generation, such as getting up from a chair, getting on and off public transport in a timely manner, climbing stairs, regaining stability after a perturbation of balance etc. (Lang et al. 2010).

Inflammation and the endocrine system

Even though undernutrition and physical inactivity can potentiate the loss of muscle mass, there are cases where muscle atrophy can occur even at energy balance due to the catabolic actions of inflammatory cytokines. This has been implied in autoimmune disorders such as rheumatoid arthritis, where inflammation-induced muscle proteolysis is evident; that is, the increased production of inflammatory agents such as the tumour necrosis factor alpha (TNF α) can lead to muscle atrophy (Rall et al. 1996). The role of C - reactive protein (CRP), interleukin 1 (IL-1) and interleukin 6 (IL-6) in muscle atrophy has since been well established, even in the absence of an autoimmune response (Molino et al. 2016). These hormones can be produced by the adipose tissue (which in this case acts as an endocrine gland) and can elicit an inflammatory response that can negatively affect muscle tissue (Cesari et al. 2005a). Particularly active in producing cytokines that can accelerate muscle breakdown are the visceral adipose cells (Schrager et al. 2007). Moreover, it has been documented that inflammation is higher in sarcopenic obese older adults compared to those with normal body compositions (Schrager et al. 2007). In the same study the researchers noted that levels of CRP, IL-1 and IL-6 were significantly associated with indices of sarcopenic obesity, such as body mass index (BMI), waist circumference (WC) and muscle strength even after adjusting for several factors such as age, gender, history of comorbidities, physical activity and smoking. The researchers thus highlighted the catabolic effect that truncal obesity can exert on muscle tissue and function through the mediation of an inflammatory

response. Moreover, it has been hypothesised that the cytokines released from the intrahepatic and intermuscular fat to local tissues may contribute, at least to a certain degree, to impaired insulin action (Molino et al. 2016). It has also been suggested that ageing *per se* is associated with a state of low-grade chronic inflammation, hence the recently introduced term ‘inflammaging’, which is regarded as a risk factor for age-associated diseases as well as morbidity and mortality (Franceschi and Campisi 2014).

Moreover, there are age-related changes in the physiological effect of anabolic hormones on the ageing body. For example, the anti-catabolic properties of insulin have been well documented as it has been proven that insulin is involved in the inhibition of muscle proteolysis (Gelfand and Barrett 1987). Wilkes et al. (2009) concluded that protein breakdown in the leg muscles in response to insulin was not attenuated in older adults to the same extent as in their younger counterparts (12% and 47% reduction in proteolysis, respectively). Therefore, this may be a sign of a diminished ability of insulin to stop muscle proteolysis with age, which indicates that older muscle is likely to experience increased muscle breakdown. Therefore, the blunted anabolic effect of insulin on the architecture of older muscle may also potentially lead to muscle atrophy (Guillet and Boirie 2005; Lonnie and Jose 2012).

Growth hormone (GH) and the insulin like-growth factor 1 (IGF-1) are anabolic peptides that are responsible, amongst others, for the growth of muscle tissue (Adamo and Farrar 2006). Their role involves triggering the proliferation and differentiation of satellite stem myocytes, resulting in increased muscle protein synthesis rates while they can concomitantly decrease the protein degradation rates (Chen et al. 2005; Fryburg 1994). Growth hormone and IGF-1 decline with age

and as an outcome older people are often deficient in these hormones (Toogood 2003). Apart from the age-related decline in these hormones, there is evidence to suggest that increased concentrations of circulating free fatty acids may exert a negative effect on the body's ability to produce these hormones (Van Dam et al. 2000), and perhaps this phenomenon is more pronounced in older adults with sarcopenic obesity compared to obesity alone (Waters et al. 2008). Testosterone is another anabolic hormone that can significantly increase the rates of muscle protein synthesis and strength (Urban et al. 1995), however, its natural production declines with age (Zumof et al. 1995; Feldman et al. 2002). Similar to GH and IGF-1, high adiposity can interfere with testosterone production in older age (Vermeulen et al. 1999), thus diminishing muscle anabolism. Therefore, a clear pattern is evident; it is not only age *per se*, but also the action of adipose tissue and inflammatory cytokines on anabolic hormones, which can have a subsequent effect on the trajectory of muscle tissue.

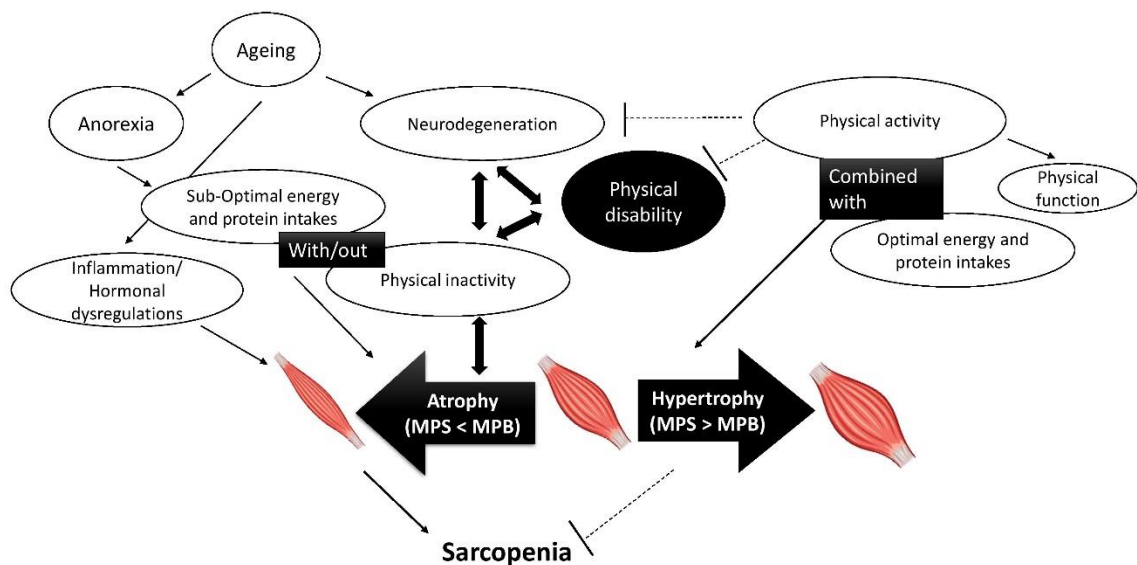


Figure 1.1 Aetiology of sarcopenia in older age. Muscle atrophy, hypertrophy and mediators (straight arrows), or inhibitors (dashed lines). When muscle protein breakdown exceeds muscle

protein synthesis, then muscle atrophy is experienced. MPS; muscle protein synthesis, MPB; muscle protein breakdown.

1.1.3 Prevalence of sarcopenia, obesity and sarcopenic obesity

In one of the first studies assessing prevalence rates of sarcopenia using appendicular skeletal muscle mass normalised to height² (two standard deviations below the respective mean of younger populations of New Mexico, US), it was found that 24% of women and 15% of men (n=883; Hispanics and Non-Hispanics) aged between 65 and 70 years were sarcopenic (Baumgartner et al. 1998). In the same study, the prevalence of sarcopenia in those aged 80+ was >50% in both sexes. In partial agreement with that finding Iannuzzi-Sucich et al. (2002) reported that 23% of Caucasian women and 27% of men from New England, US, were sarcopenic, whereas figures increased to 31% and 53%, respectively, for those aged 80 and over. In Denmark, in a group of 754 women \geq 70 years old, sarcopenia was diagnosed in 12% of them (Tanko et al. 2002). Prevalence rates of sarcopenia in Taiwan, in 302 men and women \geq 65 years Chien et al. (2008) were reported to be 26% in men and 19% in women, while no significant differences were observed between MRI and BIA-derived rates. Janssen et al. (2002) in one of the most influential studies in this field (since the regression analysis of that data generated the prediction formula for the calculation of total skeletal muscle mass from a BIA test), concluded that the prevalence rates of sarcopenia in American men and women over the age of 80 years was 50% in men and 72% in women. However, it is important to note that none of the aforementioned studies took into account muscle strength or function. According to a recent systematic review taking into account muscle strength/function as well as mass, the prevalence of sarcopenia has been reported to vary from 1 to 29% in community-dwellers and 14-33% in long-term care populations depending on the population being studied and the operational criteria (Cruz-Jentoft et al. 2014).

Similar to sarcopenia, obesity is also a growing concern due to its progressively rising prevalence rates, including in older adult populations (Porter Star et al. 2014). In 2010, approximately 35%

of adults aged 65 years or over in the US were reported to be obese (Fakhouri et al. 2012) while the respective figures in Scotland and the UK were 31% and 28%, respectively (Scottish Government 2011; Public Health England and Food Standards Agency 2014). However, these figures were based on the BMI cut-off of 30 kg m^{-2} which is likely to underestimate adiposity and also mask sarcopenia in older adults (Newman et al. 2003a). Therefore, the true prevalence of obesity in older adults is likely to be higher than the reported values, but due to scarcity of studies -especially in Scotland- this is yet to be corroborated.

Although sarcopenic obesity has gained significant attention from the scientific community in recent years, and there is a plethora of existing definitions and cut-offs for sarcopenia, obesity and sarcopenic obesity, there is no universally accepted definition (Cruz-Jentoft et al. 2010, Prado et al. 2012; Poggiogalle et al. 2014). As an outcome, depending on the definition criteria and cut-offs used the prevalence rates of sarcopenic obesity can vary up to 26-fold, which makes detection and management of the condition very challenging for healthcare practitioners (Batsis et al. 2013). To date, there are no definite figures for the prevalence of sarcopenic obesity and particularly in Scotland. In fact there is a substantial lack of studies in Scotland and the UK in general, and therefore, it is imperative that more research is conducted with a focus on sarcopenia and obesity in Scottish older adults.

1.1.4 Health consequences of sarcopenia, obesity and sarcopenic obesity

Although the financial implications of sarcopenia can place a vast burden on the public health systems (the hospitalisation costs alone for sarcopenic and sarcopenic obese patients may increase by 34% and 42%, respectively; Sousa et al. 2016) this thesis will discuss the health-related

consequences. Given the existence of a metabolic cross-talk between muscle and bone tissue and considering that muscle provides a mechanical-induced growth stimuli for bones (Cianferotti and Brandi 2013), it is not surprising that low muscle mass along with the impaired neuromuscular coordination and poor balance (the physiological mechanism of which has been discussed previously) may lead to reduced bone mineral density and increased risk of falls, osteoporosis and bone fractures. In an earlier study, 590 postmenopausal women were grouped based on their appendicular muscle mass and grip strength, and were assessed for osteopenia and osteoporosis (bone mineral density assessed by DXA) (Sjöblom et al. 2013). It was found that the sarcopenic women had a significantly higher odds ratio for osteoporosis (OR: 12.9; $p \leq 0.001$) and also, of experiencing a bone fracture (OR: 2.1; $p \leq 0.05$), compared to their non-sarcopenic counterparts. Following a similar pattern, those within the lowest quartiles for strength had significantly higher odds for osteoporosis (OR: 11.7, $p \leq 0.001$) compared to those within the highest quartiles for hand grip strength. Even after adjusting for age, BMI and other parameters such as physical activity levels the results remained significant. Similarly Szulc et al. (2005) showed that muscle mass was significantly associated with indices of bone mineral density (BMD), and those with the lowest muscle mass had low BMD and the highest risk of poor balance and falls. Moreover, apart from the direct action of muscle on bone density, there is substantial evidence supporting that chronic inflammation and potentially the metabolic syndrome (both of which may be present in sarcopenia, obesity and sarcopenic obesity) may negatively affect bone density and increase the risk of osteoporosis (Braun and Schett 2012; Zhou 2013).

With regard to glucose utilisation, muscle is the primary tissue responsible for glucose uptake via muscle-contraction and insulin-dependent pathways (Jessen and Goodyear 2005). Therefore, older people with low muscle mass are at an increased risk for type II diabetes due to poor glucose

control (Park et al. 2009). In fact, although obesity is a risk factor for insulin resistance, sarcopenia alone can exacerbate dysglycaemia regardless of the presence of obesity (Srikanthan et al. 2010). This effect can be evident particularly in older adults, given their susceptibility to muscle atrophy, which renders this a very serious consequence.

Obesity has been also associated with numerous detrimental health effects (Zamboni et al. 2005). For example, increased BMI ($>27 \text{ kg m}^{-2}$) raises the risk of mobility impairment by 2-fold in older women (Launer et al. 1994). Increased adiposity and especially abdominal obesity is an independent predictor of insulin sensitivity in old age, and according to Racette et al. (2006) it may be even more important than physical fitness. This signifies the importance of the assessment for abdominal obesity e.g. waist circumference or sagittal abdominal tissue (SAD). Similarly, Roubenoff (2006) suggested that increased fat mass, and in particular fatty tissue around the abdomen, can increase leptin and TNF α secretion, and may eventually result in insulin resistance. Moreover, adipocytes can also elicit a catabolic effect on muscle tissue, either directly through infiltration or indirectly via hormonal modulation (Cesari et al. 2005a; Schrager et al. 2007), as discussed earlier. It is quite alarming that obesity, and especially excess visceral and intermuscular adiposity, can increase the risk of type II diabetes even at normal bodyweights (Goodpaster et al. 2003).

Although the association between overweight and obesity (defined as high BMI) and higher all-cause mortality is well established in adults aged 18-65 years, the same relationship has not been fully corroborated in people over the age of 65 years (Flegal et al. 2013). According to a 97-study meta-analysis by Flegal et al. (2013), there is evidence to suggest that there may be a rightward

shift of the ‘normal BMI range’ in older age, with values around $\sim 30 - 34.9 \text{ kg m}^{-2}$ posing no extra risk in terms of all-cause mortality compared to BMIs $\sim 25 \text{ kg m}^{-2}$ in older people. Moreover, it was suggested that BMIs in the overweight range $25-29.9 \text{ kg m}^{-2}$ may in fact be beneficial by exhibiting the lowest mortality risk (Flegal et al. 2013). This phenomenon has been previously termed ‘the obesity paradox’ (Oreopoulos et al. 2009). However, the study by Flegal et al. (2013) was weakened by the absence of a model that would exclude the first years after the surveys that could be potentially affected by ‘reverse causality’. That is, it may not be BMI *per se* that affects mortality, but the presence of comorbidities at the time of the survey that have already affected the BMI and may lead to increased mortality rates in the years following the survey.

Stokes (2014), in an attempt to exclude confounders like unintentional weight loss and comorbidities at the time of the survey, used the maximum BMI that someone has been at throughout their lifespan, to assess the risk between BMI and mortality. For example, if an older person has a BMI at the time of the survey of 23 kg m^{-2} (‘current BMI’) but the maximum BMI they have ever been at was 28 kg m^{-2} (‘maximum BMI’), then the latter was used. This model excluded potential confounders related to reverse causality. The analysis indicated that all BMIs $\geq 25 \text{ kg m}^{-2}$ carried a higher risk for mortality compared to normal BMIs ($< 25 \text{ kg m}^{-2}$), when using the ‘maximum BMI’ model. In fact, overweight and obesity assessed by using the ‘maximum BMI’ accounted for 33% of mortality, compared to only 5% when the ‘current BMI’ model was used. It was also suggested that in middle-aged and older adults, normal-BMI cohorts include people at low risk (i.e. people who have maintained a healthy BMI throughout their life) as well as people at high risk (those who have lost weight unintentionally due to other comorbidities). Therefore, the use of BMI at the time of the survey cannot substantiate a reliable indication of mortality risk. This is in agreement with other research groups who have disputed the existence of

the obesity paradox and suggest that it is probably accounted for by methodological inconsistencies (Ferreira and Stehouwer 2012; Strandberg et al. 2013).

Consistent with the previous study, van Uffelen et al. (2010) analysed the data from more than 11,000 older women (≥ 70 yr) and noted that BMIs 25-27 kg m⁻² carried the lowest mortality risk, whereas BMIs 22-24 kg m⁻² carried the lowest risk of hospital admissions. In the same study, the risk of heart disease and type II diabetes increased (almost linearly) with increasing BMIs above 18.0 kg m⁻², whereas risk of hypertension increased above 18.5 kg m⁻² but it tended to plateau at BMIs > 30.0 kg m⁻².

The obesity paradox has been recently disputed with robust methodologies and large scale data coming from a meta-analysis by Bowman et al. (2016). That analysis incorporated the Clinical Practice Research Datalink (CPRD) data from 995,031 adults ≥ 60 years registered with primary care in England (2000-2014). The initial results suggested that higher BMIs (25-35 kg m⁻²) may indeed place no added risk on mortality, however, when the first four years of the follow up were excluded from the analysis (that is, only years 4 to 14 were analysed) it was found that the lowest mortality risk was for BMIs ~ 23 -26.9 kg m⁻². In general, BMIs over 25 kg m⁻² increased the hazard ratio (95% CI) from 1.03 (0.97 – 1.09) in the 60-64 years group for BMIs ≥ 25 kg m⁻² to 1.80 (1.62 - 2.00) for a BMI ≥ 40 kg m⁻² in the 70-74 group. In a sub-analysis for the incidence rates of type II diabetes and coronary heart disease (CHD) the risk increased for BMIs ≥ 27 kg m⁻², across all age groups.

The complexity of this issue has been previously highlighted by Romero-Corral et al. (2010) who stated that body composition in older age can vary to such a degree that high adiposity can be present even at normal bodyweights, which implies that older people can have high body fatness and therefore low muscle mass even at normal BMIs. In cases of normal BMIs, it is very challenging for a physician to detect high adiposity and/or low muscle mass, and therefore it is dubious whether a change in lifestyle would be recommended by health professionals.

Therefore, although the detrimental consequences of sarcopenia on health are well documented, and there is a relative agreement on the consequences of overweight and obesity (at least for BMIs $\geq 27 \text{ kg m}^{-2}$), the effects of sarcopenic obesity have not been fully elucidated. This is mainly due to the scarcity of studies with sarcopenic obese populations, a lack of a robust definition and diagnostic criteria, as well as the issues implicated with the use of BMI in obesity classification. As a result some authors have reported that the combination of sarcopenia with obesity work synergistically in creating a health-deteriorating phenotype whereas others have conferred that sarcopenic obesity does not carry a higher risk compared to those of obesity or sarcopenia alone.

For example in an 8-year prospective study, Baumgartner et al. (2004) noted that sarcopenic obesity predicted more physical impairments (e.g. decline in gait speed, balance) and falls than either obesity or sarcopenia alone. An Instrumental Activities of Daily Living (IADL) questionnaire was used to assess physical capacity, DXA for body composition and participants were included only if they were highly functional at baseline, which allowed the onset of physical impairments to be followed up. This finding however does not concur with Davidson et al (2002) who suggested that those in the highest quintiles for % body fat as well as those with high BMIs

($\geq 30 \text{ kg m}^{-2}$) have a higher risk for physical disabilities, but those with low muscle mass combined with obesity (i.e. sarcopenic obese) were not presented with a greater risk for mobility limitations compared to obesity alone. That study was, however, a cross-sectional analysis of associations between body composition (measured indirectly by anthropometry) and physical capacity assessed by a 5-item questionnaire of daily activities and thus could only offer a ‘snapshot image’ of the associations at the time of the survey. Apart from methodological differences that may account for these discrepancies (e.g. different cut-offs derived by DXA vs anthropometry, different questionnaires, and a prospective vs cross-sectional design), it could also be hypothesised that there are additional factors, other than absolute muscle mass and fat mass, that may play an important role in mobility performance, e.g. distribution of fat, muscle density, strength, power and quality (Goodpaster et al. 2001; Fielding et al. 2011). For example, a higher muscle mass does not directly translate into higher strength and functional improvements, in fact in some cases gains in muscle mass may not even attenuate the decline in strength (Goodpaster et al. 2006). Therefore, when examining changes and differences in functional parameters it is important to consider factors such as muscle strength and quality, in addition to absolute changes in body tissues.

In terms of cardiovascular risk factors, the relationship between sarcopenic obesity and hypertension has also been assessed in a study with 2,099 men and 2,747 women ≥ 60 years (Han et al. 2014). After adjusting for factors including age and gender, physical activity, lipid profile, smoking status and alcohol consumption, the analysis revealed not only that sarcopenic obese presented the highest prevalence of hypertension (approximately 74.7% vs 49.7% in non-obese non-sarcopenic, 60.9% in non-obese sarcopenic, and 66.2% in obese non-sarcopenic; $p < 0.001$) but also the highest OR. Namely, the non-obese sarcopenic, obese non-sarcopenic and sarcopenic obese groups had an OR (95%CI) of 1.5 (1.23–1.84), 2.08 (1.68–2.57) and 3.0 (2.48–3.63,

$p < 0.001$), respectively. Moreover, BMI, %BF, WC and appendicular skeletal mass adjusted for weight (ASM/weight) were all significantly associated with blood pressure (all the aforementioned factors were positively associated with blood pressure, except ASM/weight which showed a negative association). When a separate analysis was conducted based on the presence of type II diabetes, the sarcopenic obese group presented again the highest ORs across all groups, and in fact the diabetic sarcopenic obese group had the highest OR of all [3.95 (2.51–6.20)]. Consistent with the previous finding, Park et al. (2013) showed that sarcopenia and obesity may act synergistically in increasing blood pressure in a study with 6,832 adult participants. The OR (95% CI) for obesity, sarcopenia and sarcopenic obesity was 3.15 (2.76–3.59), 2.48 (1.89–6.16) and 6.42 (4.85–8.48), respectively.

Chung et al. (2013) assessed the impact of body composition on several cardiometabolic risk factors, such as blood pressure, lipid profile, glucose tolerance, metabolic syndrome and Vitamin D deficiency. For comparison purposes the researchers divided all participants [2,943 older adults (≥ 60 years)] into four groups based on the presence of sarcopenia (ASM/weight regardless of strength/function) and obesity ($\text{BMI} \geq 25 \text{ kg m}^{-2}$) in a similar pattern to the previous studies. The prevalence of metabolic syndrome was significantly higher in the sarcopenic obese group in both men and women (60.9 and 71.1%, respectively, $p < 0.001$) compared with the rest of the groups. In men, the sarcopenic obese group was characterised by significantly higher levels of fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) compared with the rest of the groups. Moreover, the sarcopenic obese group had significantly higher systolic and diastolic pressure, fasting glucose, triglycerides and HDL cholesterol compared with the healthy group. Accordingly in women, the sarcopenic obese group had significantly higher levels of fasting glucose compared with the sarcopenic non-obese group and higher fasting insulin, HOMA-

IR compared with the non-sarcopenic obese group. This highlights that sarcopenia with obesity can potentiate insulin resistance and increase the risk for type II diabetes. Further, the sarcopenic obese groups exhibited the lowest vitamin D concentrations [25(OH)D: 18.5 ± 7.1 ng mL⁻¹] which were significantly lower than those of the non-sarcopenic non-obese (20.5 ± 7.8 ng mL⁻¹) and the non-sarcopenic obese (20.9 ± 7.6 ng mL⁻¹) (both $p < 0.001$). Those results, although derived from a cross-sectional analysis underline the importance of body composition in cardiometabolic health. However, one interesting finding that could account for some of the differences (or confound the results), was that adults with sarcopenia were less likely to participate in exercise training compared with their non-sarcopenic counterparts, and as such measurements of strength/function would offer a more complete understanding of the associations.

The importance of strength in relation to CVD risk was noted by Stephen and Janssen (2009) who followed prospectively a cohort of 3,366 older community-dwellers, dividing them into two groups for sarcopenic obesity a) high waist circumference with low muscle mass and b) high waist circumference with low muscle strength. Participants were followed for eight years in order to determine their CVD risk. An interesting finding related to the previous discussion about the usefulness of BMI, was that the mean body mass index of the sarcopenic obese group (high WC + low muscle) was 27.1 ± 2.4 kg m⁻². That underlined again the possibility of older adults having increased central adiposity and sarcopenia even at BMIs < 30 kg m⁻². Moreover, the risk of congestive heart failure and CVD increased by 42% and 23%, respectively, in the obese group with low strength but not in the obese group with low muscle mass. That finding suggested that strength, may account for some of the discrepancies observed in the literature. However, when the results were adjusted for age, sex, ethnicity, income, physical activity, alcohol consumption, smoking, and cognitive function there was no significance in the CVD risk factors between the

groups. In agreement with the previous finding, Atkins et al. (2014) noted that the CVD risk may not be significantly higher in sarcopenic obese vs healthy older adults, nevertheless, when sarcopenic obesity is defined as abdominal obesity with sarcopenia (derived by low mid-arm muscle circumference), then the all-cause mortality risk for the sarcopenic obesity group can be significant with an HR (95%CI) of 1.44 (1.10–1.90) (after adjusting for age, physical activity, smoking, alcohol, social status and CVD risk factors such as inflammatory markers).

A potentially important parameter that is often overlooked is the dietary profile and especially protein intake. Kim et al. (2015) assessed the 10-year CVD risk in 3,320 middle-aged and older Koreans after categorising them into four groups based on the presence of sarcopenia (ASMI lower than 1SD below the normal values of a healthy 20-40 years group) and obesity ($\text{BMI} \geq 25 \text{ kg m}^{-2}$). In the 10-year follow-up test the crude CVD risk was highest in men and women in the sarcopenic obese and the sarcopenic non-obese groups compared with the healthy and non-sarcopenic obese groups. Protein intakes and sessions of resistance exercise were significantly higher in the non-sarcopenic groups regardless of obesity. When the CVD risk was adjusted for protein intake, exercise participation, alcohol consumption and income, the risk for the sarcopenic obese group remained significant, with the odds ratio (OR) (95%CI) for sarcopenic obese men and women being 2.49 (1.53-4.06) and 1.87 (1.02-3.41), respectively.

Apart from CVD risk, sarcopenic obesity may also affect the psychological status of older adults, which can be a vital parameter in older age. Ishii et al. (2016) conducted a study assessing the prevalence and sarcopenic obesity-associated risk of depression in 1,731 Japanese older adults (>65y) using a geriatric depression scale and categorising participants into four groups based on

the presence of sarcopenia (low ASMI) and obesity (highest sex-specific quintile for %BF). The highest prevalence of depression was reported in the sarcopenic obese group (~26%), whereas it ranged between 8.5-11% in the other three groups. In addition, the odds ratio (OR) for depression was statistically significant only in the sarcopenic obese group [OR (95%CI) = 3.63 (1.96-6.71), $p < 0.001$] whereas this was even more pronounced in the 65-74 years group [OR (95%CI) = 6.05 (1.89-19.38), $p = 0.003$] even after adjusting for several factors, such as sleep quality, food intake, physical activity and comorbidities.

Clinical prognosis

Sarcopenic obesity may also affect clinical prognosis in chronic disease patients. In a thorough review Biolo et al. (2014) provided a wealth of evidence supporting that changes in body composition and especially a reduced muscle mass alone or concomitant to fat gains can lead to poor prognosis for a wide spectrum of conditions ranging from chronic obstructive pulmonary disease (COPD) to several types of cancer, even at normal BMIs. Choudhary et al. (2015) concluded that the prevalence of metabolic syndrome in sarcopenic obese patients after liver transplantation was significantly higher compared to their non-sarcopenic obese counterparts (57% vs 20%, $p < 0.05$). In cardiac surgery patients, the existence of low muscle with high fat mass can increase the risk of adverse health effects, such as post-operative infection by ~28% [odds ratio (95%CI): 7.9 (1.2-54.1)] (Visser et al. 2013). This figure is quite alarming considering that approximately one out of four surgical procedures in the UK involve patients at or over the age of 75 years (Griffiths et al. 2014), and out of ~158,000 deaths due to CVD in the UK in 2015, almost 90% of them were accounted for by people ≥ 65 years (BHF 2017a). It is also noteworthy that out of the six regions with the highest mortality rates in the UK, four of them are in Scotland (BHF 2017b).

In a cohort of 328 end-stage renal disease (ESRD) patients with a mean (\pm SD) age of 52 (\pm 12) yr, it was found that both high fat mass index and low lean mass index were associated with high inflammation in sarcopenic obese patients (Honda et al. 2007). Furthermore, the patients with sarcopenic obesity showed a tendency towards higher prevalence rates of diabetes and CVD. In the same study, high fat mass and low muscle were independently associated with a pronounced inflammatory response, however, sarcopenia was a stronger predictor of mortality.

In cancer patients, muscle atrophy is a strong predictor of lower/shorter survival (Martin et al. 2013). It has been repeatedly documented that sarcopenic patients are likely to encounter health complications and poor prognosis in various stages of cancers of the lung (Tsukioka et al. 2017), liver (Iritani et al. 2015), colon (Lieffers et al. 2012), colorectal (Huang et al. 2015), skin (Sabel et al. 2011) and pancreas (Tan et al. 2009). On the other hand obesity alone not only can increase the risk for certain types of cancer (e.g. colorectal by >30%; Ma et al. 2013) but also for post-operation complications (recurrence of cancer and/or mortality; Bardou et al. 2013). Therefore, it is not surprising that older cancer patients exhibiting both sarcopenia and obesity upon hospital admission are predisposed to suboptimal outcomes and poor clinical prognosis (Gonzalez et al. 2014; Carneiro et al. 2016).

Fujiwara et al. (2015) demonstrated that low muscle index, intramuscular fat deposition and visceral adipose tissue were all independently and significantly associated with mortality, with a hazard ratio HR (95% CI) of 1.52 (1.18-1.96), 1.34 (1.05-1.71) and 1.35 (1.09-1.66), respectively. Further, Fujiwara and colleagues showed that BMI was only weakly associated with intramuscular

fat ($r = 0.19 - 0.25$) and visceral fat ($r = 0.23 - 0.26$) and thus, it may not be an appropriate proxy for individual body composition assessments. It is not surprising therefore, that sarcopenic obesity was an independent predictor of mortality [HR: 4.2 (2.4 – 7.2)] and significantly associated with poor functional outcomes in patients with tumors in the gastrointestinal and the respiratory tract (Prado et al. 2008). In the last study, it was also suggested that sarcopenic obesity was an independent predictor of survival and could also exacerbate chemotherapy-induced toxicity. That effect is likely accounted for by the fact that the chemotherapy drugs are usually hydrophilic agents primarily metabolised in the lean soft tissue, i.e. the muscle and liver (Carneiro et al. 2016). Similarly, a study by Mei et al. (2016) reported an increased risk of infection and lower survival after surgery for gastrointestinal cancer in sarcopenic obese patients.

The previous studies provide clear evidence to support the theory that high adiposity accompanied by, and often masking, sarcopenia can exacerbate the adverse effects of cancer and/or cancer treatments on health (Carneiro et al. 2016). Following up on the previously discussed topic regarding the use of BMI and the misleading notion of the obesity paradox, Gonzalez et al. (2014) demonstrated that in cancer patients the obesity paradox exists only when obesity is defined as high BMI, but not when using body composition proxies such as the fat mass index measured by bioelectrical impedance (Gonzalez et al. 2014). Therefore, it was concluded that in the presence of low muscle, high adiposity can offer no improvement in survival rates. That finding is in agreement with Kalantar et al. (2012) who suggested that direct body composition indices such as muscle mass are better predictors of mortality than BMI.

In summary, body composition and strength/function in older age are of vital importance. Not only does an association exist between body composition and the onset, progression and/or prognosis of other conditions such as type II diabetes, CVD, and cancer, but also, the capacity to perform physical activities can affect (and be affected by) these conditions, with physical inactivity exacerbating the loss of muscle and function, while promoting adiposity. This vicious cycle can lead to disability, institutionalization and consequently increased mortality rates. Although the importance of this condition has been documented, it is unknown what percentage of the older population is affected by sarcopenia and obesity in Scotland, with data existing currently only for BMI-derived obesity rates and only very limited information is available about sarcopenic obesity. Moreover, in order to reduce the health risks associated with sarcopenic obesity and increase the chances of healthier and quality years in older age, interventions should be implemented with multi-factorial approaches against both the deterioration of body composition as well as the attenuation of physical decline.

1.2 Management strategies for sarcopenic obesity in older age

Decreasing body fat while increasing muscle mass and physical function may not only have beneficial effects on body composition and functionality, but also may potentially reduce the risk of clinical conditions such as hypertension, dyslipidemia, insulin resistance, metabolic syndrome, diabetes and cancer, while also improving quality of life (Garatachea et al. 2015). These health benefits will be discussed in this section along with documented lifestyle paradigms focusing on nutrition and exercise training.

1.2.1 Exercise & Physical activity

Physical activity can be defined as any activity that involves muscular contraction and raises energy expenditure (American College of Sports Medicine; ACSM 2014). Exercise is a structured form of physical activity with specific frequency, intensity, type and duration aiming at increasing certain aspects of physical fitness such as strength, power, flexibility and cardiovascular capacity (ACSM 2014). Garatachea et al. (2015) in a thorough review presented how exercise can elicit beneficial effects on the musculoskeletal, neuromuscular, cardiovascular, respiratory and cerebrovascular systems and can attenuate the manifestations of the main ‘hallmarks’ of ageing. The physiological adaptations of different types of exercise as well as their metabolic pathways at genetic, cellular and molecular level have also been reviewed thoroughly by (Konopka and Harber 2014; Garatachea et al. 2015; McGlory and Phillips 2015). In this section, focus will be placed mainly on the potential for exercise training to induce body composition and functional changes, since they may influence the progression of sarcopenic obesity.

1.2.1.1 Effects of exercise on body composition and function

It has been long documented that exercise can improve body composition and strength/function in young and older adults. One of the first studies to report changes in muscle mass and strength was that by Frontera et al. (1988). Twelve weeks of resistance exercise (three weekly sessions at 80% of a maximum repetition-1RM) resulted in significant increases in leg strength (ranged from 107.4 to 226.7%, $p<0.001$), total thigh muscle area (11.4%, $p<0.01$) and fibre type I and II areas (by 33.5% and 27.6%, respectively, $p<0.01$ in both) in adults 60-72 years of age. Similar increases in frail older adults (mean age 90 ± 1 yr), after strength training (three times weekly, at 80% 1RM) for eight weeks, were documented for strength (average improvement in knee extension was $174\pm 31\%$) and thigh muscle area (by $9.0\pm 4.5\%$) (Fiatarone 1990). In that trial, a decrease in quadriceps strength by 32% was noted within four weeks after the conclusion of the training period (also known as detraining effect) (Fiatarone 1990). In a study with 1,644 men and women 21-80 years old, the effects of 10-week exercise training based on the guidelines produced by the American College of Sports Medicine (ACSM) were assessed (Westcott and Winett 2006; Westcott 2009). The gain in lean mass and loss of fat mass were on average 1.4 kg and 1.7 kg, respectively. Sub-group analyses found that men and women gained on average 2.1 kg and 1.2 kg of lean tissue, respectively.

One of the key studies that provided information on body composition and energy expenditure in sedentary adults aged 56-80 yr was conducted by Campbell et al. (1994). The exercise protocol involved 3x30 min strength training per week for a total of three months. The results indicated a significant increase in lean mass (1.4 ± 0.4 kg, $p<0.01$) and a concomitant decrease in fat mass (1.8 ± 0.4 kg, $p<0.001$). Moreover, significant increases in strength (upper and lower body strength tests showed increases of 22-94%), resting metabolic rate (~15%) and energy expenditure were

reported (~7%). Resting metabolic rate was significantly and positively correlated to lean mass at baseline ($r=0.86$, $p<0.001$) and after the exercise training period ($r=0.85$, $p<0.001$). Consistent with this observation, Pratley et al. (1994) reported similar changes in lean mass, fat mass, strength and resting metabolic rates (~7.7%) after a strength training protocol. The same research group also noted that resistance exercise may result in significantly increased resting metabolic rates even when combined with a weight loss regimen in postmenopausal women (Ryas et al. 1995).

In a 12-month study with post-menopausal women ($n=39$, 50-70 yr), resistance exercise was found to be effective in significantly increasing total muscle mass (by 1.2 ± 0.4 kg vs -0.5 ± 0.8 kg) and strength (several upper and lower body tests showed a significant increase in the exercise group, whilst a decline or no change was observed in the control) as well as dynamic balance measured by backward tandem walk ($+8.5\%$ in exercise vs -14.3% in control, $p=0.005$) (Nelson et al. 1994). Moreover, the exercise group experienced a significant increase in lumbar spine bone mineral density (BMD) ($+1.0\%$ vs -1.8% in control, $p=0.04$) and femoral neck BMD (by $+0.9\%$ in exercise vs -2.3% in control, $p=0.02$) (Nelson et al. 1994). Therefore, it was suggested that resistance exercise can decrease the risk of bone fractures. Indeed, it has long been documented that poor strength, balance and bone mineral density are risk factors for falls and fractures amongst older individuals (Tinetti et al. 1988).

The interaction ('crosstalk') between muscle and bone tissue is well-established (Maurel et al. 2017). Thus, it has long been postulated that strong muscles usually complement strong bones (Hughes et al. 1995). More recently it has also been shown that a significant association also exists between leg power and bone mineral density (BMD) of the hip even after adjusting for weight,

height, smoking, and leisure time (Schwarz et al. 2014). The bone-muscle link is especially evident in athletes, who are likely to experience a greater (BMD) and bone mineral content (BMC) in the extremities of the dominant side compared to the non-dominant, which is indicative of the anabolic effect exerted by the exercising muscles on bone architecture (Haapasalo 1994).

Menkes et al. (1993) showed that a 16-week strength training programme can increase bone mineral density in older adults at the femoral neck (by 3.8%, $p < 0.05$) and the lumbar spine (by 2%, $p < 0.05$). A similar increase in femoral BMD (2.8%) was noted after a 16-week strength training programme in men ($n=21$, age= 61 ± 1 yr) (Ryan et al. 1994). The positive effect of exercise training on BMD of men across all ages > 31 years has also been confirmed by a meta-analysis. An increase of $\sim 2.6\%$ in BMD can be expected at the sites loaded during the resistance exercise training (Kelley et al. 2000). Endurance training can also prevent the approximate loss of 1% in BMD per year in femoral and lumbar sites in pre- and post-menopausal women (Wolff et al. 1999). Nonetheless, it is important to note that this effect is likely to be experienced by women who consume adequate amounts of calcium; the threshold of which is theorised to be ≥ 1000 mg daily (Specker 1996; Wolff et al. 1999). Moreover, based on a meta-analysis of 29 studies, resistance exercise has also been found to be beneficial in increasing BMD in femur, lumbar spine and radius in post-menopausal women (Kelley et al. 2001).

Aerobic training improves the body's potential to utilise oxygen more efficiently. The benefits of aerobic exercise on the cardiovascular system have been extensively documented (Fleg 2012). Similar to resistance training, aerobic exercise can also attenuate the energy restriction-induced BMD losses in older women (Pritchard et al. 1996; Ryan et al. 1998). More importantly, an

important benefit of aerobic exercise in older people that has been under-reported is its ability to enhance muscle hypertrophy and function (in addition to augmenting aerobic capacity). In a 12-week study with older women (71 ± 2 yr) exercising at a cycle ergometer (intensity was progressively increased from 60 to 80% heart rate reserve), it was shown that quadriceps volume and power of the knee extensor increased by $12 \pm 2\%$ ($p < 0.05$) and $55 \pm 7\%$ ($p < 0.05$), respectively (Harber et al. 2009). The biopsy analysis showed a preferential increase in the size and power of type I muscle fibres. Similar results were obtained in a subsequent study with older men (74 ± 3 yr) (Harber et al. 2012). Twelve weeks of cycle ergometer training resulted in significantly higher quadricep volume by $6 \pm 1\%$ ($p < 0.05$) (which was comparable to increases noted in a group of young exercisers). That increase in muscle volume was accounted for by an increase in the cross-sectional area of type I myofibres. However, contrary to women, the peak power of both type I and IIa was increased in older men, indicating that there may be sex-specific differences in physiological responses to aerobic-based exercise (Harber et al. 2012).

Power (velocity of force development) is an important determinant of body's functionality and may decline at higher rates than strength in older adults (Skelton et al. 1994; Metter et al. 1997). Muscle power may be a better predictor of functional status than absolute strength in older age (Foldvari et al. 2000). Power and speed of muscle contraction is especially important for older adults, since it is involved in virtually all functional movements performed in everyday activities, from getting up from a chair quickly, to crossing the road swiftly, changing direction to avoid obstacles/accidents, getting to the restroom in time etc. (vanBeveren 2012). Power training (increasing the speed of performed movements) has therefore been regarded as a beneficial type of training. Power training can augment muscle mass (Nogueira et al. 2009) and power as well as strength comparably to or even better than traditional strength training (Marsh et al. 2009).

Another way of increasing power is by performing plyometric exercises. Plyometric training includes movements that initially lengthen the muscle (eccentric contraction) and then swiftly shorten it (concentric contraction). They can be used to increase power in lower and upper extremities of the body and similar to power training, they can enhance bone formation and consequently increase BMD (Stengel et al. 2005).

Furthermore, with advancing age the body adopts a certain posture based on movement patterns and positioning. Often this posture results in certain muscles being continuously held in a shortened or lengthened status, which can subsequently result in muscular stiffness and poor balance (Gajdosik et al. 2004). This is particularly noticed in sedentary older adults who do not engage in physical activities and thus do not perform movements at a full range of motion. Therefore, stretching is often included in training programmes for older adults, as it can increase the range of motion for the targeted joints and alleviate the imbalances in muscle length (Feland et al. 2002). Nevertheless, it is important to note, that even in the absence of stretching exercises, strength training alone can improve flexibility in older individuals (Barbosa et al. 2009).

Other effective forms of exercise include functional training or task-specific exercise (TSE). Functional training refers to movements that require the individual to use multiple joints and move through multiple axes of motion challenging his or her balance and proprioception (VanBeveren and Avers 2012). This can be done by changing direction or plane of movement, change speed, keep the eyes open or closed, by moving the head to different directions while avoiding obstacles etc. Task-specific training is a form of functional training that requires the engagement of multiple joints and simulates everyday activities, such as getting up from the chair, stair climbing etc. This

type of training is considered an effective way of improving strength and balance within a context of practicality (Buford et al. 2014). Task specific training has significantly reduced the time needed to perform a series of tasks related to bed-rise and chair-rise in congregate housing residents ($n=161$, ≥ 65 yr) (Alexander et al. 2001), whereas it has been found equally effective to resistance exercise in terms of improving the performance of activities of daily living (ADL) (de Vreede et al. 2004).

Therefore, training paradigms incorporating different modalities (e.g. strength, power, balance, daily tasks-simulation exercises, flexibility etc.) would in theory be beneficial for older adults with sarcopenic obesity. However, such studies are scarce and the aforementioned ones were performed in specific conditions (e.g. in a gym or physiology lab) with specialised equipment and/or at high intensities which may have low practicality for community-based interventions targeting at older adults with an established deterioration of body composition. Moreover, secondary to functional and body composition improvements, a knowledge gap exists as to whether exercise can elicit health-related benefits which are particularly important for the sarcopenic obese, e.g. inflammation, abdominal fat deposition, mental status, etc.

1.2.1.2 Health benefits of Exercise

Exercise training has the potential to elicit a protective effect against CVD and type II diabetes. In older adults (66 ± 8 yr) with diabetes, resistance exercise (twice a week at 60-80%RM for 16 weeks) has been found effective in improving glycemic control (and reduced the dose of diabetes medication) as well as increasing fat free mass ($+1.2 \pm 0.2$ kg) and reducing truncal fat mass (-0.7 ± 0.1) and systolic blood pressure (-9.7 ± 1.6 mmHg) (Castaneda et al. 2002). While both aerobic and

resistance exercise alone can improve glycemic control, when combined they showed a synergistic potential superior to either training type alone in 251 middle aged and older adults (Sigal et al. 2007). Twenty two weeks of aerobic (60-75% HRmax) plus resistance exercise (2-3 sets at maximum weight that can be lifted for 7-9 reps) can reduce glycated haemoglobin (HbA1c) significantly more than either of them alone. The aerobic, resistance and combined groups experienced a reduction in percentage points in HbA1c concentration by -0.43 (95%CI; -0.70 to -0.17), -0.30 (-0.56 to 0.05) and -0.90 (1.15 to -0.64), respectively.

Although exercise (especially resistance) can acutely increase blood pressure, it has also positive effects on both systolic and diastolic pressure (Baechle and Westcott 2010). In a study with 1,644 adults aged 21-80 years, a combination of 20 min aerobic and 20min resistance training performed (two or three times weekly) reduced systolic and diastolic blood pressure by ~4 mmHg and ~2 mmHg, respectively (Westcott 2009). Even in hypertensive patients exercise can produce modest reductions in blood pressure, however, the combination of exercise with a weight loss regimen and antihypertensive drugs may be the optimal approach for those with moderate to severe hypertension according to Ehsani (2001). Indeed, this has been confirmed in randomised control trials with older adults who usually experience reductions in blood pressure after exercise training alone (2-7 mmHg), and these reductions were significantly associated with body composition changes and especially fat losses from the central region (Stewart et al. 2005; Barone et al. 2009).

One other potential benefit of resistance exercise is the anti-depressant effects that it can exert on older adults. Singh et al. (2001) conducted a 20-week long RCT employing a resistance exercise routine (n=32, 71.3± 1.2 yr). They concluded that depression scores were significantly reduced in

the intervention group (weight-lifting) compared with the control group (no exercise). Moreover, six weeks after the programme had been finished, 33% of the intervention group was still taking part in exercise sessions compared to 0% from the control group. Considering that depression may be more prevalent in sarcopenic obese older adults than their healthy counterparts (Ishii et al. 2016), this anti-depressant effect of exercise can be of vital importance for the mental status of this population group.

Albeit this has yet to be confirmed in human studies, exercise has shown a potential in attenuating the impairments in autophagy mechanism that are often associated with advancing age and sarcopenia (Kim et al. 2013b). Moreover, exercise can decrease the inflammatory response and the increase in intermuscular fat depots usually involved in conditions associated with ageing (Petersen and Pedersen 2005; Marcus et al. 2010).

1.2.1.3 Physical Activity Guidelines

According to the World Health Organisation (WHO), most of the health burden in older age can be accounted for by risk factors for chronic diseases such as cancer and CVD (WHO 2009). Physical inactivity is the fourth overall risk factor for death, affecting all income classes especially in middle- and high-income countries. Hypertension, smoking and hyperglycaemia are the first three risk factors, whereas overweight and obesity come fifth (WHO 2009). The leading causes of death in older people are heart disease and cancer whereas dementia is another leading risk factor after the age of 80 (Centres for Disease Control and Prevention 2014; Office for National Statistics 2015). Lack of physical activity can increase the risk of CVD, breast and colon cancer as well as stroke, type II diabetes, depression and obesity (Health and Social Care Information Centre 2013).

Regular participation in physical activities (either in the form of structured exercise training or by increasing the levels of habitual physical activities) has been associated with higher functional status. Physical activity can also reduce the risk of physical disability and may potentially reduce the risk of dementia in older adults (Paterson and Warburton 2010) as well as improve cognitive function (Tseng et al. 2011). In addition, it can reduce the risk of CVD mortality even among those with a high-risk metabolic profile or existing CVD (Hamer and Stamatakis 2009; Hamer and Stamatakis 2012).

According to a joint document produced by the four UK Chief Medical Officers (Department of Health 2011), there is substantial evidence to suggest that an inverse dose-response relationship exists between physical activity and risk of stroke, type II diabetes and cancers of breast and colon in older adults. Moreover, regular physical activity can reduce the risk of anxiety, depression and dementia and improve strength, balance and bone mineral density while reducing the likelihood of falling and bone fractures. The physical activity recommendations for older adults are presented in **Table 1.2** (adapted from '*Start Active, Stay Active*'; Department of Health, 2011). The document suggests that some physical activity is better than none, however, the aim for all older adults should be to stay as active as possible and minimise the periods of inactivity. The UK physical activity guidelines are in accordance with the respective guidelines published by the American College of Sports Medicine (**Appendix 1**; ACSM 2014). Namely, the ACSM recommends a total of 150-300 min of moderate-intensity aerobic activities or 75-100 min of vigorous intensities (ACSM 2016).

Table 1.2 UK Exercise and Physical activity guidelines for older adults

- Participation in moderate-intensity activities for at least 150 minutes weekly, which do not necessarily need to be continuous but in bouts of 10+ minutes (e.g. five sessions of 30 minutes each). Example activities: cycling, walking, dancing.
- For those who already exercise at moderate intensities, it is recommended to try activities of vigorous intensity lasting 75 minutes spread throughout the week or a combination of moderate and high-intensity activities. Example activities: running, tennis
- Activities aiming at improving strength should be undertaken at least twice a week. Example activities: Strength exercises for all major muscle groups e.g. legs, hips, back, shoulder, arms, abdominals.
- Those at risk of falling should undertake activities aiming to improve balance and coordination at least twice a week.
- Avoid long periods of inactivity as it is an independent ill-health risk factor.

Notes: adapted from the document ‘Start Active, Stay Active’ produced by the UK Chief Medical Officers (Department of Health 2011).

1.2.1.4 Current physical activity levels and sedentary behaviours

The recommendations suggest that older people should perform at least 150 minutes of moderate-intensity physical activities per week. However, according to data from the ‘Health survey for England, 2012’, the ‘Scottish health survey, 2014’, the ‘Welsh health survey, 2015’ and the ‘Health Survey Northern Ireland 2013/14’ as collated and presented by the British Heart Foundation National Centre (BHFNC 2016) report low compliance (**Table 1.3**). Namely, in Scotland only marginally more than half (51%) of the 65-74 age group follow the guidelines, whereas the respective figure for the 75+ group falls to 26%. Moreover, 53% of men and 56% of women from the 75+ group have reported very low physical activity levels, performing less than 30 minutes of physical activity per week. In England, only 47% and 20% of the 65-74 and 75+ groups, respectively, follow the guidelines. In Wales, although the proportion of the older population meeting the guidelines is slightly higher (**Table 1.3**), 40% of the overall 65+ group does less than 30 minutes of physical activities and has therefore been classified ‘inactive’. In

Northern Ireland, even more alarming than the low physical activity levels (**Table 1.3**) is the fact that only 1% of the over 75s performs activities at least twice a week in order to improve muscular strength.

Along with the declining levels of participation in physical activities is the increasing amount of time that older people spend in conditions that require very low energy expenditure (other than sleeping), such as sitting or lying, which are known as sedentary behaviours (BHFNC 2012). Such behaviours may include sitting and lying while at home or work, while socialising with others or while watching TV/reading a book, and commuting (BHFNC 2012). The time spent in sedentary behaviours is very important because it has been consistently associated with all cause mortality irrespective of physical activity levels (Proper et al. 2011; Thorp et al. 2011). In Scotland, amongst all adult age groups (19 years old and over), the 65-74 and 74+ groups are the most sedentary, spending an average of 6.5 and 7.5 hours, respectively, on sedentary behaviours during weekdays, whereas in weekends the figures are even higher (6.7 and 7.6 hours, respectively) (Scottish Government 2013). Similarly, in England the most sedentary among the adults groups are those over the age of 65 years, with approximately 6.0, 6.4 and 6.7 of daily sedentary hours for the 65-74, 75-84 and 85+ groups, respectively (Health and Social Care Information Centre 2013). Furthermore, the English older adults with a BMI over 25 kg·m⁻² are likely to spend on average more sedentary hours than their counterparts of a normal BMI (Health and Social Care Information Centre 2013). Additionally, English older adults from deprived areas and low incomes tend to spend more time on sedentary behaviours. This finding is in agreement with a study conducted in Scotland in 2009 reporting that a lower socioeconomic status is associated with increased periods of time spent on sedentary screen-based entertainment (e.g. watching television) (Stamatakis et al. 2009). Nonetheless, there is limited evidence to provide full understanding of how the

environmental and sociocultural factors affect the sedentary behaviours in older adults (BHFNC 2012a).

Table 1.3 Proportion of the older populations that meet the PA guidelines in the UK.

Country	Age group	
	65-74	75+
England	Women 42%	Women 13%
	Men 51%	Men 30%
Scotland	Women 44%	Women 22%
	Men 59%	Men 32%
Wales	Total 56%	Total 35%
Northern Ireland	Total 28%	Total 12%

Notes: Data from the British Heart Foundation National Centre (BHFNC 2016)

1.2.1.5 Contraindications to exercise in older adults

In general, exercise training is safe for most individuals and at any age, however, there are a few medical conditions where specific contraindications may exist and can prevent an older person from participating in exercise training (Panton and Loney 2011). These conditions may include uncontrolled and severe cognitive or psychological problems, terminal illnesses, or conditions that can affect the cardiac, lung and/or vascular function such as ischemia, a recent myocardial infarction, cardiac dysrhythmias, unstable angina, severe aortic stenosis, uncontrolled heart failure or other acute cardiac event, aneurysm, pulmonary embolus or infarction, or other serious acute systemic infections (Panton and Loney 2011).

Moreover, avoiding exercises –at least temporarily- may be indicated for conditions that do not allow for a proper and safe performance of the exercises such as eye conditions (e.g. retinal

bleeding, cataract), hernias or joint injuries. It is important to note that conditions such as osteopenia or osteoporosis, arthritis, diabetes, stroke, depression, peripheral vascular disease are not by themselves a contraindication to exercise; in fact exercise can offer health benefits and improvements that may not be attainable through drug treatment alone (ACSM 2009).

In addition, even though exercise carries an inherent risk of transient musculoskeletal injuries, in the long term it can significantly increase strength, gait speed and endurance, improve the metabolic profile and reduce the risk of CVD, as well as reduce the risk of falls and fractures in older people, all of which outweigh the potential risks. Moreover, the risk of death for older people who do not engage in exercise on a regular basis is higher than their fit counterparts (Kokkinos 2012). The only exception may be death due to cardiac arrest during exercise training in older individuals with existing coronary heart disease. Nevertheless, even within the older population groups chances of cardiac arrest due to exercise are relatively low (Kokkinos 2012). It is also important to note that older adults do not necessarily need to perform high-intensity workouts to obtain the health benefits of exercise. Exercising at moderate intensities has been consistently proven beneficial in reducing the risk of obesity, type II diabetes, arthritis, heart disease and some forms of cancer, especially of breast and colon (Panton and Loney 2011). Furthermore, becoming fit by exercising initially at low intensities followed by gradual increases may reduce the risk of cardiac events (Riebe et al. 2015).

1.2.2 Nutritional Strategies

The two most popular nutritional strategies that have been documented to affect body composition and function include modification of the macronutrient profile, with a particular emphasis on protein and energy intakes. Energy-restriction diets in particular, are regarded as the cornerstone of weight-loss regimens (Klein et al. 2001).

1.2.2.1 Energy-restriction diets

One of the most extensively studied paradigms for the treatment of obesity is intentional weight loss via dietary energy restriction. Although the benefits of weight loss in obese older adults with regard to reducing mortality rates are still inconclusive (and possibly are accounted for by the differences in research protocols and diagnostic criteria as discussed previously), it is evident that voluntary weight loss via caloric restriction can reduce several obesity-related risk factors for CVD and metabolic syndrome, such as insulin resistance, dyslipidaemia and raised blood pressure (Klein et al. 2001; Poirier et al. 2006).

In a study including 35 older women (age: 69 ± 8 yr; BMI: 30.97 ± 6.38 kg m⁻²), following a moderate energy restriction regimen (500 kcal daily deficit) for three months, it was reported that central adiposity measured by waist circumference (WC) and sagittal adipose depth (SAD) was significantly and positively associated with fasting glucose and insulin levels, HOMA-IR, high sensitivity CRP (hs-CRP), subcutaneous adipose tissue and intramuscular fat deposition (assessed by CT scan at mid-thigh level) and negatively associated with high density lipoprotein (HDL) cholesterol (Mazzali et al. 2006). After the 3-month caloric deficit, body weight (-4.66 ± 2.72 kg), BMI (-1.95 ± 1.17 kg.m⁻²), SAD (-1.62 ± 0.98 cm) total fat mass (-3.2 ± 2.03 kg) and

intramuscular adipose tissue ($-2.15 \pm 1.59 \text{ cm}^2$) all declined significantly ($p < 0.001$). Insulin and HOMA-IR were also significantly reduced ($p < 0.05$), however, hs-CRP did not show a significant change, although there was a decrease from baseline to 3-months follow-up [from 2.90 (2.0–3.60) mg L^{-1} to 2.50 (1.90–3.70) mg L^{-1}]. Nevertheless, it appears that the study was powered to detect changes in body composition, but underpowered for hs-CRP, since other studies with similar weight and fat mass changes, noted significant declines in median hsCRP from ~ 1.80 to 1.40 mg L^{-1} or even from ~ 0.7 to 0.6 mg L^{-1} but in considerably larger cohorts, $n > 700$ (Nicklas et al. 2013; Kitagawa et al. 2017). Moreover, the clinical significance of changes in hsCRP depends also on the baseline values, since a concentration of $> 2 \text{ mg L}^{-1}$ is believed to be linked to increased risk of stroke and CVD in Caucasians (Meschia et al. 2014) whereas in Asians the cut off may be lower at $\sim 1 \text{ mg L}^{-1}$ (Kitagawa et al. 2017).

Bouchard et al. (2007) examined the relationship between body composition and physical capacity in 904 older men and women. Their findings revealed a significant negative association between % body fat and balance (1-leg stand), walking speed and overall physical capacity in both men and women. Moreover, older adults who are obese may be less responsive to exercise-induced functional improvements compared with their non-obese counterparts (Manini et al. 2010). This may be accounted for by the increased deposition of adipose cells between/within muscles that can affect muscle quality (Hausman et al. 2014) and/or by the increased effort required to move the extra mass. For example, as we age there are certain muscles that are particularly susceptible to the accretion of intermuscular fat, such as the gastrocnemius, which can impair mobility and physical performance (Tuttle et al. 2012). It has been hypothesised therefore, that fat losses can enhance physical performance. Energy restriction alone (daily deficit of 500-750kcal for 12 months) has been effective in augmenting physical function in obese frail older adults. In that

study body weight decreased by ~10 kg (~3 kg and ~7 kg were lost from lean deposits and fat stores, respectively) (Villareal et al. 2011a). The time needed to complete a walking task was reduced by 10%, while the time participants could stand on one leg increased by 40%. Additionally, a 14% increase was noted in the ‘physical’ component of the health related quality of life questionnaire, SF-36. Despite the loss in lean mass, the improvement in physical function can be attributed to the decreased mechanical burden on the joints, the improved lean mass to fat ratio and the decreased effort required to move the extra mass. Indeed, it has been estimated that for every pound of weight lost there is a 4-fold reduction in the mechanical load applied on the knee joint per step (Messier et al. 2005).

Similar reductions in body weight after a moderate caloric restriction (<500 kcal daily deficit) have also been confirmed in an older study by Katznel et al. (1995). It was noted that nine months of reduced energy intake can reduce body weight by ~9.5 kg, while improving fasting glucose and insulin levels by 2% and 18%, respectively. Moreover, glucose and insulin areas under the curve (AUC) were reduced by 8% and 26%, respectively, during the oral glucose tolerance test. In addition, high-density lipoprotein (HDL) was increased significantly by 13%.

Apart from improving the metabolic profile and functional capacity, diets restricting energy intake (from as low as 8% up to 30-40%) are regarded as one of the most effective ‘anti-ageing strategies’ since they have the potential to lower the accumulation of senescent cells and reduce the age-related inflammatory response (Phillips and Leeuwenburgh 2005; Marzetti et al. 2008 Franceschi 2016). In a cross-over study design a modest caloric restriction (~20% below energy requirements), significantly attenuated the inflammatory response over 14-day periods of bed-rest

and ambulatory conditions at a eucaloric vs. a hypocaloric state (Bosutti et al. 2008). In the control phase (participants receiving a eucaloric diet matching energy expenditure) IL-6 and CRP plasma levels were significantly higher ($p=0.01$ and $p=0.04$, respectively) as was the ratio of IL-6: IL-10 ($p=0.001$) compared with the hypocaloric phase. Interleukin-10 is an anti-inflammatory marker with a potential health benefit, primarily by inhibiting the production of pro-inflammatory hormones including but not limited to: IL-1, IL-6 and TNF α (Petrovani 1999). As discussed at the beginning of this chapter even less than two weeks of inactivity can promote muscle atrophy (Breen et al. 2013) and one of the potential factors accounting for that effect may be the increased secretion of inflammatory hormones. Although these results reveal a potential for caloric restriction to attenuate inflammation, these results are yet to be confirmed in sarcopenic obese older adults.

In a study with 41 postmenopausal sedentary and obese women (54 ± 1 yr, 34.8 ± 1.2 kg.m⁻²) a daily energy intake of ~1,250 kcal over a 12-week period resulted in significant loss in total body weight, fat mass and trunk fat mass ($p<0.001$ for all) (Figuerola et al. 2013). However, more than one kg of lean mass was lost ($p=0.03$) due to the energy restriction regimen. The energy deficit-induced lean mass loss is a common phenomenon in energy restriction regimens and therefore raises questions about their effectiveness in adults with sarcopenia.

Thus, although caloric restriction alone may be a viable weight loss strategy, it is debatable whether it is the optimal approach for sarcopenic obese older adults. It has been estimated that the energy deficit-induced weight loss in obese individuals can be accounted for by ~75-80% fat losses and ~20-25% lean mass losses (Ballor et al. 1988). In a 52-study systematic review of energy

restriction with/without exercise in adults (age ≥ 50 yr, BMI ≥ 25 kg m⁻²), Weinheimer et al. (2010) concluded that 81% of the studies adopting a calorie-deficit protocol noted losses in lean mass (more than 15% of the losses were from lean mass). Even when energy deficit was combined with exercise, the same degree of lean mass losses was apparent in 39% of the studies. Therefore, the challenge with management strategies for sarcopenic obesity is to promote reductions in fat mass while concomitantly preserving (or increasing if possible) muscle mass and function.

1.2.2.2 Dietary protein

The beneficial effects of protein may be accounted for by its potential for increased thermogenesis which combined with its satiating properties (Latner and Schwartz 1999) makes protein the most ‘calorie-for-calorie efficient nutrient’ in terms of appetite control (Arentson-Lantz et al. 2015). It has been documented that increasing protein intake from 15% to 30% can lead to a decrease in ad-libitum energy intake, which can result in significant weight and fat losses even after 12 weeks (Weigle et al. 2005). The lean mass (including muscle and bones) sparing effect of protein may be explained by the protein-induced activation of the mTOR pathway and increased IGF-1 concentration (a detailed review of this pathway has been presented by McLeod et al. 2016). As discussed earlier IGF-1 concentrations decline with age. However, a study employing protein supplementation (20 g daily) resulted in increased levels of IGF-1 in older adults with a recent hip fracture (Schurch et al. 1998). The authors also suggested that the increase in IGF-1 possibly also accounted for the attenuation of bone mineral losses and the shorter hospitalisation period.

In addition, a high-protein meal may result in a lower inflammatory response compared to an isocaloric carbohydrate-rich meal (Parvaresh-Rizi et al. 2016). Provision of a meal rich in

carbohydrates exerted a negative effect on immunometabolic responses by increasing the inflammatory response, which may indicate a greater risk of CVD. Albeit in younger adults, that study also confirmed that the obese and insulin-resistant individuals are more susceptible to these carbohydrate-mediated negative effects compared to their lean and insulin-sensitive counterparts. That finding could be particularly useful for dietary interventions with older sarcopenic obese individuals, since the latter may be more susceptible to insulin resistance.

Protein intake during energy restriction

Although caloric restriction is likely to result in losses of lean mass, it has been hypothesised that increased intakes of dietary protein have the potential to attenuate this loss even during energy restriction. In a 12-week study employing an energy restriction protocol (~500 kcal daily deficit), a higher protein intake (16% vs 25% of daily energy intake) resulted in significantly lower lean mass losses (-1.5 ± 0.3 vs -0.1 ± 0.3 , $p < 0.03$) in overweight adults aged 20-65 yr (Farnsworth et al. 2003). Moreover, although the overall weight lost was similar in both groups (~8 kg), the glycemic response (glucose area under the curve) and triacylglycerol levels were significantly lower in the high protein group. In a study with 100 obese men, a diet providing $2.2 \text{ g protein} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$ was compared against a lower protein diet ($1.1 \text{ g} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$), while both groups were on an energy deficit diet plan (500 kcal daily deficit) (Treyzon et al. 2008). Both groups lost the same amount of weight, however, the high-protein group lost preferentially more body fat compared to the low-protein group ($-1.65 \pm 0.63 \text{ kg}$ vs $-0.64 \pm 0.79 \text{ kg}$; $p < 0.05$).

Indeed, a meta analysis of 24 trials ($n=1,063$) by Wycherley et al. (2012) confirmed this hypothesis stating that during energy deficit periods shifting the protein: carbohydrate ratio towards higher

protein intakes (at $\sim 1.25 \text{ g} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$) can have favourable effects on body composition. Namely, this shift can promote weight loss through greater losses of fat (and a higher satiety response noted in most of the studies) whilst attenuating the decline in lean tissue and resting energy expenditure. Therefore, a higher protein intake may be a valuable modifiable parameter in nutritional interventions aiming to decrease fat depots while preserving muscle mass, however, the effectiveness of such paradigms has not been evaluated in sarcopenic obesity.

Intriguingly, higher protein intakes achieved through increased consumption of dairy products may facilitate greater losses of fat mass during short-term energy-restriction interventions (Chen et al. 2012). Although in premenopausal women, a study by Josse et al. (2011) showed that increased protein and especially dairy protein (30% of energy intake was from protein and half of it was from dairy sources) can augment lean mass while concomitantly lowering body fat, during energy-restriction combined with exercise training, in overweight and obese participants. That study was also one of the first to show an association between a decline in visceral adipose tissue and increased protein and calcium intakes.

Protein-induced augmentation of muscle mass and strength

Although debatable to date, when protein is combined with exercise training (resistance training in particular) it may significantly increase lean mass as well as strength. According to a meta-analysis 22 of studies with young ($n=462$, age <50 yr) and middle aged/older adults ($n=218$, age >50 yr) protein supplementation (daily average of $42 \pm 30\text{g}$ protein) can increase lean mass (95%CI) by 0.69 ($0.47, 0.91$) kg ($p < 0.001$) and leg strength by 13.5 ($6.4, 20.7$) kg ($p < 0.005$) (Cermak et al. 2012). The improvements in muscle and strength in the middle-age/older subgroup

during a 3-month training period were calculated to be on average 38% and 33%, respectively. Nevertheless, there are key information that are yet to be fully elucidated such the effectiveness of high protein diets to ameliorate body composition and function in sarcopenic obese adults.

There is evidence supporting the notion that protein ingestion after exercise training can significantly enhance muscle protein synthesis rates in both young and older adults (Pennings et al. 2011a). Pennings et al. (2011a) examined the effect of ingestion 20 g protein in 24 older adults (74 ± 1 yr) after a single session of resistance and moderate-intensity aerobic training and observed that *de novo* muscle protein synthesis in older adults was significantly increased compared to rest-states. However, that effect was assessed in an acute setting and therefore long term implications were not fully explored. In a continuation of their previous findings, Pennings et al. (2012) assessed the impact of various protein intakes taken in a bolus dose on muscle protein synthesis. They compared the muscle protein synthetic effect of 10, 20 and 35 g of whey protein in 33 healthy older adults (73 ± 2 yr). The results revealed a dose-dependent increase in amino acid absorption and muscle accretion with the 35 g promoting a significantly higher anabolic response compared to the lower doses ($p < 0.005$). In a similar fashion, Yang et al. (2012) conducted a study comparing the effects of 0, 10, 20 and 40 g whey protein ingestion after a single bout of resistance exercise ($n=37$, 71 ± 4 yr). Only the groups receiving 20 g and 40 g experienced significant responses in MPS, with the 40 g group exhibiting significantly higher MPS than the 20 g group (95% increase vs 60%, $p < 0.05$). Although protein ingestion was explored in an acute setting, these studies made it apparent that protein supplementation after exercise can significantly enhance synthesis of new muscle tissue in older age. However, the ceiling effect in terms of muscle accretion in older adults is still not well defined.

In an attempt to further understand the effect of protein timing on muscle hypertrophy and strength Schoenfeld et al. (2013) conducted a systematic review and meta-analysis of trials employing protein supplementation protocols. Their findings disputed the importance of protein timing and indicated that the only significant driving factor for both muscle hypertrophy and strength was the total amount of protein consumed per day. Therefore, they suggested that as long as adequate amounts of protein are consumed throughout the day (and exercise training is involved) then ingesting protein during or immediately post-workout will exert no additional benefit. Perhaps this finding may account for the lack of significant improvements in some protein studies. For example, in a 12-week study Candow et al. (2006) assessed the effect of protein timing (0.3g protein.kg bw⁻¹ pre-workout vs post-workout) on muscle size and strength in older men. The main finding was that training alone accounted for improvements in strength and size, regardless of the protein supplementation and timing. However, it was apparent that baseline intakes were already high (1.2-1.5 g. kg bw⁻¹.day⁻¹) which may explain the lack of additional benefit.

Regarding the type of protein, Burd et al. (2012) conducted one of the first studies assessing the effect of 20 g whey vs 20 g casein on muscle protein synthesis in older men. Whey elicited a significantly higher synthetic response both at rest and after exercise compared to casein. That finding was possibly accounted for by the significantly higher aminoacidaemia and leucinaemia observed after ingestion of whey. That shows an anabolic potential for essential amino acids (EAAs) and particularly leucine. Indeed, researchers have shown that the anabolic response to acute protein feeding may be blunted in older adults unless the leucine content of the meal is ≥ 2.8 g or the total EAA content is 10 g to 20 g (Cuthbertson et al. 2005; Katsanos et al. 2006). In a

study including 24 healthy older adults, coingestion of 20 g casein with 2.5 g leucine elicited significantly higher MPS rates by 22% ($p < 0.05$) compared to 20 g casein alone (Wall et al. 2013). With regard to the role of leucine in muscle anabolism, it has been known that leucine can increase MPS rates by activating the mechanistic target of rapamycin – complex 1 (MTOR1) pathway, which is responsible for the initiation of the muscle hypertrophy cascade; more key information about this mechanism have been presented by Wolfson et al. (2016).

1.2.2.3 Protein requirements, recommendations and current intakes

Recommendations and Requirements

The current recommended dietary allowance for protein for all adults and regardless of age is $0.8 \text{ g} \cdot \text{kg} \text{ bw}^{-1}$ in the US and Canada (Institute of Medicine of the National Academies 2005; Campbell et al. 2008) whereas the UK recommendations advise for $0.75 \text{ g} \text{ protein} \cdot \text{kg} \text{ bw}^{-1}$ (British Nutrition Foundation 2017). This is in agreement with the joint report of the World Health Organization (WHO 2007), which suggested an intake $\sim 0.8 \text{ g} \cdot \text{kg} \text{ bw}^{-1}$ to be safe and adequate to meet the requirements for protein of 97.5% of the adult population.

These figures have been principally derived from nitrogen-balance studies assessing the protein requirements of the healthy adult population (Rand et al. 2003). Rand et al. conducted a systematic review of 19 N-balance studies with 235 participants (however, only one study included older adults) and concluded that the mean daily protein requirements in adults were $\sim 0.65\text{--}0.83 \text{ g} \cdot \text{kg} \text{ bw}^{-1}$. However, researchers have questioned the applicability of N-balance in certain sub-groups of the population such as the older sarcopenic obese, since these studies do not take into consideration several conditions (such as health status, hospitalisation, injury, surgery etc) that

can profoundly affect protein requirements (Wolfe et al. 2008; Pedersen and Cederholm 2014). Sarcopenia may be a very slow process that can take years to develop and eventually lead into impaired function and increased risk of morbidity and mortality (Pedersen and Cederholm 2014). Indeed most of the N-balance studies have used short duration protocols (~10-30 days). Moreover, they have assessed protein requirements in healthy population groups. Campbell et al. (2008) using the N-balance method concluded that the daily protein requirements for older adults are $\sim 0.8 \text{ g} \cdot \text{kg} \text{ bw}^{-1}$ and do not differ significantly to those of young adults. However, the authors acknowledged and discussed thoroughly the limitations of the N-balance protocols and why they should be interpreted with caution. In a more recent review Volpi et al. (2013) suggested that N-balance studies can provide an indication of the minimum average requirements for protein of the general healthy population. However, the figures derived from such studies do not necessarily reflect the optimum protein intakes that can maximise function in older adults with sarcopenia or other conditions associated with muscle atrophy. Therefore, new and reliable protocols need to be developed to define more accurately the so called ‘optimal intakes’.

Recent studies using different techniques such as the indicator amino acid oxidation (IAAO) have noted that older men and women may require higher protein intakes than what was previously believed (Tang et al. 2014; Rafii et al. 2015; Rafii et al. 2016). Rafii and colleagues have suggested that the protein recommendations for older adults appear to be underestimated by $\sim 30\%$ and as such they should be increased to $\sim 1.25 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \text{ day}^{-1}$. Nonetheless, long-term intervention studies modulating the dietary protein content in sarcopenic obese adults are scarce and the majority of data come from observational studies.

In a 3-year follow-up cohort study with 2,732 healthy older men and women (aged 70-79 yr), the mean protein intake of the cohort was $0.9 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ (Houston et al. 2008). More importantly, at the 3-year follow up those in the lowest quintiles for protein intake ($0.7\text{-}0.8 \text{ g} \cdot \text{kg} \cdot \text{bw}^{-1} \cdot \text{day}^{-1}$) experienced ~40% higher losses ($p < 0.05$) of lean mass and appendicular lean mass compared to those in the highest quintiles ($1.0\text{-}1.1 \text{ g} \cdot \text{kg} \cdot \text{bw}^{-1} \cdot \text{day}^{-1}$). This may explain why some people experience higher loss of lean mass over the years. In a 10-year longitudinal study Vellas et al. (1997) assessed the effect of protein intake on several health indices in 304 healthy older participants. One of the most interesting findings was that those consuming protein at $1.2\text{-}1.76 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ tended to have fewer health problems during the 10 years follow up period compared to those with intakes $< 0.8 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$. In terms of function, in one of the few randomised controlled trials conducted in older frail adults, an increase in protein consumption from $1.0 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ to $1.4 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ significantly improved muscle function (Tieland et al. 2012a).

Consequently, in older individuals it has been recently agreed that protein recommendations should be actually higher than those for the general population, and in the range of 1.0 to $1.2 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ (Bauer et al. 2013). Intakes of $\sim 1.5 \text{ g} \cdot \text{kg} \text{ bw}^{-1} \cdot \text{day}^{-1}$ or even higher are recommended for undernourished or sarcopenic older adults who engage in exercise programs and want to optimise protein intakes for the associated health and function benefits (Wolfe et al. 2008; Deutz et al. 2014).

Current Intakes in the UK

According to the national diet and nutrition survey (NDNS; GOV UK 2014) the mean daily energy intake in 2012 was 1930 kcal in men and 1482 kcal in women. The absolute daily protein intakes

for men and women (>65 yr) were 77.6 g and 63.8 g, respectively, contributing to the total daily energy intake by approximately 17% in both. Overall, the most substantial contribution to protein intakes can be attributed to meat and meat products (32%), milk and dairy products (17%), fish and fish products (11%), cereal products (22%), vegetables and potatoes (8%) and eggs (3%).

It is important to mention that absolute dietary amounts should be interpreted with caution since these values are based on self-reported dietary intakes. When the method of doubly labelled water (DLW) was used to compare self-reported energy intake with total energy expenditure the former was found to be 29% lower than the latter, therefore this needs to be taken into consideration when interpreting these results (GOV UK 2017).

Moreover, it should be taken into consideration that body mass trends show a rightward shift towards higher body weights, but the relative protein intakes ($\text{g} \cdot \text{kg} \text{ bw}^{-1}$) of older adults have not been thoroughly studied. Therefore, the relative protein intakes have not been corroborated neither for the general population nor for the sarcopenic obese. Existing data from studies in older obese and frail older adults suggest that protein intakes in these groups are likely to be lower than 'optimal'. Tieland et al. (2012b) noted that more than 10% of the healthy community-dwellers and 30% of the older frail adults, consumed less than $0.7 \text{ g} \cdot \text{kg} \cdot \text{bw}^{-1}$ per day.

Therefore, it could be hypothesised that sarcopenic and/or sarcopenic obese older adults do not consume adequate protein in their diet, which may affect the size as well as the quality of the musculature. In theory an increased protein intake alongside an exercise programme could

potentially offer benefits to that population group, and particularly to those embarking on weight loss programmes. However, it is currently unknown what the intakes of sarcopenic obese adults are (and particularly in Scotland), and whether interventions introducing increased protein intakes can be beneficial either in terms of body composition or physical function improvements.

1.2.2.3 Adverse effects of high protein intakes

The evidence to support that daily intakes of protein up to at least 1.2 to 1.5 g · kg bw⁻¹ are safe for older people with no pre-existing kidney conditions has been consistent (Pedersen and Cederholm 2014; Witard et al. 2016a). Increasing protein intakes (from 1.0 g to 1.4 g · kg bw⁻¹ · day⁻¹) alongside a resistance-exercise programme has significantly augmented lean mass and function in older adults without affecting renal function or causing any health-related side effects in a study by Tieland et al. (2012c). Albeit not statistically significant, an improvement in glomerular filtration rate (GFR) was noted when protein supplementation was combined with resistance exercise in older adults (Ramel et al. 2013). This is in agreement with Mikusova et al. (2016) who noted that increasing daily protein intakes from 1.0 to 1.5g · kg bw⁻¹ combined with exercise training over a period of 6 months resulted in a small but significant increase in GFR in sarcopenic older adults (+1.0 (IQR: 2.8, 4.2) mL/min/1.73m², p=0.01) whereas no difference was observed in the control group (isocaloric supplement). Furthermore, even those who support the hypothesis of a link between high protein intakes and impaired kidney function agree that these effects may be proved in intakes > 2-3g · kg bw⁻¹ (Marckmann et al. 2015).

The impact of protein consumption on bone health has been a topic of debates due to the raised urinary calcium that follows increased protein intakes; however, at the same time protein can a)

provide amino acid precursors which can maintain bone architecture b) aid calcium absorption and c) potentially increase IGF-1 and muscle mass, and thus promote bone health (Darling et al. 2009; Thorpe and Evans 2011). Those who support the notion that chronically elevated protein intakes may impair bone health are basing their claim on a theory hypothesising that bone minerals are dissolved from the bone site to neutralise the amino acid-induced acidity (Vormann and Goedecke 2006). However, this view has been rejected by prospective studies, literature reviews and meta-analyses which have substantiated that neither an 'acid-loading' diet nor an alkaline one can be detrimental or protective on bone health, respectively (Fenton et al. 2010; Fenton et al. 2011; Bonjour 2013). In addition, one systematic review (Pedersen and Cederholm 2014) and one meta-analysis (Darling et al. 2009) have concluded that there is no substantial evidence to support causality between protein intake and reduced bone mineral content/density or fracture risk in older adults. On the contrary, there is a small but significant protective effect of dietary protein intake on bone physiology, by increasing mineral density at the lumbar site (Darling et al. 2009). When all factors are taken into consideration, it has been suggested that if calcium intake is adequate, then increasing protein intakes is not likely to be harmful for bone health and it can even offer modest benefits (WHO 2007; Darling et al. 2009; Thorpe and Evans 2011). This opinion is in accordance with a prospective study of 20,035 Norwegian men and 19,752 women, which reported no association between hip fractures and non-dairy protein intake. When both protein and calcium intake were taken into account, only the group in the highest quartile for non-dairy protein and the lowest quartile for calcium intake) exhibited a significantly higher relative risk for fracture (1.9, 95%CI [1.09-3.56]) (Meyer et al. 1997).

Emerging evidence has raised questions about the existence of a link between protein (and particularly whey protein) with an impaired glucose response and insulin resistance. A study by

Smith et al. (2015) suggested that ingestion of whey protein ($0.6 \text{ g} \cdot \text{kg fat free mass}^{-1}$) may induce insulin resistance in sedentary post-menopausal women as it can blunt the insulin-induced glucose uptake by the muscles (and this effect was not accounted for by a leucine-mediated mTOR activation). Although this was a very important finding, it was based on an acute study comparing water (control group) against ingestion of whey protein and therefore, for more robust conclusions to be drawn, long-term studies are essential, and possibly more types of protein need to be tested (e.g. casein, albumin). In response to the aforementioned study, Dioguardi (2015) commented that the alanine and arginine amino acids-components of whey protein may be responsible for the observed effect, however, it was suggested that long-term supplementation with all EAAs is likely to improve insulin sensitivity. In middle-aged overweight and obese adults, 12-week supplementation with whey protein significantly improved the metabolic profile (lowered triglycerides, total and LDL cholesterol) and decreased HOMA-IR and fasting insulin when compared against isocaloric glucose supplements (Pal et al. 2010). In acute trials ingestion of whey protein has also been proven effective in improving glucose control in type II diabetic participants after a high GI meal (21% blood glucose reduction was noted after whey protein vs pork meat) (Frid et al. 2005). This effect was accounted for by a significantly higher insulin secretion after ingestion of whey. In a large scale 9-month RCT ($n=220$) combining consumption of different quantities of whey (0,10,20,30 g twice daily) with resistance and aerobic training, it was shown that whey protein had no significant effect on HOMA-IR, insulin sensitivity index or glucose area under the curve (AUC) (Weinheimer et al. 2012). The only difference was a significantly lower AUC for insulin between baseline and post-intervention, noticed in all groups and was independent of protein supplementation. Interestingly, although protein intakes increased in some cases up to $\sim 150 \text{ g day}^{-1}$ or 1.6 g day^{-1} no changes in GFR were noted in any of the groups.

1.2.3 Vitamin D

Vitamin D is an important, fat-soluble micronutrient essential for physiological functions throughout the lifespan. Vitamin D is either synthesised in the skin via direct exposure of skin to UV sunlight or taken via dietary sources in the form of Vitamin D₂ or Vitamin D₃ and gets converted to 25-hydroxyvitamin (25(OH)D). The latter is then hydroxylated into the biologically active form of Vitamin D, which is 1,25-dihydroxyvitamin (1,25(OH)₂D) (MacLaughlin and Holick 1985). Although the biologically active form of vitamin D is 1,25(OH)₂D, according to the UK Scientific Advisory Committee for Nutrition (SACN) the most reliable assessment of vitamin D blood status is performed based on serum 25(OH)D levels as it can better reflect the availability of vitamin D from both endogenous and exogenous sources (SACN 2016). This stands true because 25(OH)D has a long half-life, it is not tightly regulated by homeostatic mechanisms and in addition, because the circulating levels of 25(OH)D are 1000-fold higher than those of 1,25(OH)₂D (SACN 2016; Wagatsuma and Sakuma 2014).

There are several cut-offs for deficiency, insufficiency and optimal levels of blood Vitamin D. For example the Scottish Food Standard Agency and SACN, define deficiency as levels <25 nM (or 10 ng/L), whereas levels >25nM are considered to be sufficient for normal functioning (Purdon et al. 2013; SACN 2016). The Institute of Medicine (IOM) has stated that levels <50 nM (or 20 ng/L) may not be sufficient for everyone (Ross et al. 2011), whilst others have suggested that the optimal levels of serum 25(OH)D are >75 nM (or 30 ng/L), insufficient between 50 and 75 nM and deficiency should be defined as serum levels <50 nM (Hollick 2007).

1.2.3.1 Vitamin D in older age

Vitamin D deficiency, assessed by serum 25(OH)D levels, is prevalent on a global scale, affecting approximately 1 billion people (Holick 2007). Older people are more susceptible to low vitamin D levels due to low dietary vitamin D intake, reduced skin exposure to sunlight and also due to reduced capacity of the aged skin to synthesise vitamin D (MacLaughlin and Holick 1985). Vitamin D deficiency in older individuals is associated with decreased bone mineral density, muscle atrophy, low muscle strength, increased risk of falls and bone fractures and increased risk of mobility limitations and disability (Snijder et al. 2006; Ceglia 2008; Houston et al. 2013; Sanders et al. 2014). Given that 90% of the bone fractures occur after a fall, it is not surprising that vitamin D supplementation has been regarded as an important element in many areas of geriatric therapy (Sanders et al. 2014).

In the UK, according to a report from 2005, 9.6% and 15% of men and women, respectively, over the age of 65 years living in private UK households were found to be deficient (Hirani and Primates 2005). A more recent systematic review assessing the effectiveness of vitamin D supplementation without the addition of exercise in people over 60 years, concluded that daily oral administration of 800-1000 IU (20-30 mcg) of Vitamin D had beneficial effects on strength and balance (Muir and Montero-Ontas 2011). For sarcopenic obese older adults, it has been suggested that, doses higher than 1,000 IU vitamin D/day may be required (Villareal et al. 2011a). In fact, doses as high as 50,000 IU per week have been administered to obese subjects suffering from Vitamin D insufficiency and protein malnutrition (Baer 2013).

A longitudinal study by Okuno et al. (2011) in pre-frail older participants showed that a 3-month exercise intervention resulted in significant improvements in timed-up-and-go tests only in those with serum levels of 25 (OH) vitamin D ≤ 45 nM, while those with serum value >47.5 nM did not experience any significant improvements. It was also suggested that serum levels ≥ 67.5 nM are preferable if the aim is improvements in physical fitness. Consistent with this notion, a meta-analysis by Stockton et al. (2011) reported a significant effect of vitamin D on strength only in those with serum levels <25 nM. Kim et al. (2011) indicated that Korean sarcopenic individuals exhibit lower levels of serum 25 (OH)D compared to their non-sarcopenic counterparts. Additionally, in a similar study, the researchers noted that older sarcopenic obese Koreans had lower concentrations of 25 (OH)D and higher HOMA-IR and CRP levels than their non-sarcopenic obese counterparts (Kim et al. 2013a).

In 2007, 90% of the UK adult population were found to have insufficient serum 25 (OH) vitamin D (<75 nM) during winter and spring, whereas this figure fell to 60% for the summer months (Hyppönen and Power 2007). In the same study, obese participants had a 2-fold increased risk of vitamin D hypovitaminosis than non-obese participants. Similarly, Scottish participants were twice as likely to have serum levels ≤ 40 nM compared with the rest of the UK.

1.2.3.2 Association of vitamin D hypovitaminosis with sarcopenic obesity

Vitamin D can affect the bone metabolism by regulating a) the gut calcium and phosphorus absorption and b) the activity of osteoblasts and osteoclasts (Christakos et al. 2003). Similarly, it can affect muscle function a) in the short term by regulating the intramuscular calcium influx

required for muscle contraction and b) in the long term by preventing muscular atrophy (Sanders et al. 2014).

Vitamin D deficiency may play a negative role in the development/progression of sarcopenic obesity by promoting adipogenesis, muscle atrophy and an increased inflammatory response (Sanders et al. 2014). This is in accordance with Wagatsuma and Sakuma (2014) who based their findings on epidemiological and clinical trials, and supported that vitamin D can affect the musculoskeletal function and architecture, the inflammatory response and the metabolic profile of older adults, all of which can potentially affect the development of sarcopenia and obesity.

Chronic inflammation can contribute to muscle atrophy and increased adiposity. Peake et al. (2010) and Girgis et al. (2013) have provided substantial evidence supporting the argument that vitamin D status may impact upon signalling pathways responsible for the regulation of inflammation in older people. This has also been suggested in clinical trials by Schleithoff et al. (2006) and Van den Berghe et al. (2003) who showed that Vitamin D supplementation may suppress the production of CRP, TNF α and IL-6 and increase the anti-inflammatory hormone IL-10.

One other potential mechanism through which Vitamin D can be beneficial for older people is the reduction in intra- and intermuscular adipose tissue (IMAT) deposition (Scott et al. 2013). Although this has not been fully elucidated, research has shown that IMAT increases with age and is one of the most important predictors of muscle quality and performance in older adults (Visser et al. 2005). It has been suggested that one possible mechanism involves the differentiation of muscle cells to adipose cells (Ryan et al. 2013). In muscle cells lines, low concentrations of

vitamin D (simulating deficient states in humans) have resulted in increased adipogenesis via increased transdifferentiation of myocyte precursors into adipocytes (driven possibly by up-regulation of the peroxisome proliferator-activated receptor gamma2 (PPAR γ 2) (Ryan et al. 2013). In normal and supra-physiological concentrations of Vitamin D this effect was suppressed.

A systematic review and meta-analysis noted that individuals with a high serum 25(OH)D concentration may have 43% lower risk of developing type II diabetes, however, the exact mechanism was not fully elucidated (Mitri et al. 2011). Wagatsuma and Sakuma (2014) have suggested a theory based on which Vitamin D can potentially modulate the expression and translocation of the Glucose Transporter type 4 (GLUT-4) through insulin-dependent and insulin-independent pathways. GLUT4 is responsible for the transport of glucose into muscle cells and adipocytes and there is evidence to suggest that expression of GLUT4 is increased in the presence of 1,25(OH) $_2$ D which can result in increased glucose utilisation (Manna and Jain 2012). Another potential mechanism for the modulation of glucose intake involves the regulation of mitochondrial metabolism via activity of the NADH oxidase and catalase enzymes (Kukal et al. 2016). In that study it was shown that the uptake of glucose depends on the presence of vitamin D, with higher concentrations of 25(OH)D resulting in higher activity for the aforementioned enzymes. The notion of an improved oxidative function of the mitochondria has also been supported by Sinha et al. (2013) who noted that vitamin D resulted in improved oxidative capacity in severely deficient (25(OH)D<15nM) adults. In that study 20,000 IU vitamin D were administered on alternate days for 10-12 weeks and resulted in reduced recovery times for phosphocreatine and adenosine diphosphate (ADP) as well as lower fatigue.

Daily administration of 4000IU vitamin D3 for 4 months has been shown to increase muscle fibre cross-sectional area and intramyonuclear vitamin D receptor concentration (particularly in type II fibres), in a randomised control trial with older women, experiencing insufficient vitamin D levels at baseline (25-60 nM) and limited mobility (Ceglia et al. 2013). This finding is in agreement with Sato et al. (2005) who supported that even lower doses of vitamin D2 (1000IU day⁻¹) administered over a 2-year period to older female stroke survivors can significantly increase the number and size of type II muscle fibres as well as muscle strength. These studies highlight a potential link that may exist between vitamin D and mechanisms that control muscle hypertrophy.

1.2.3.3 Vitamin D status of older adults in the UK

A previous study of 99 patients who attended an Edinburgh medical healthcare practice reported that only 2% had optimal serum [25(OH)D] (>75nM), whereas 45% had severe deficiency (<25 nM) (Rhein 2008). In a subsequent report those with severe deficiency complained of pains, aches, tiredness and bad mood, but usually reported improvements after receiving Vitamin D supplementation (Rhein 2014). In 2013, the Scottish Food Standard Agency collated information from the 2010-11 Scottish Health surveys and reported that the older Scottish adults had an average serum concentration of 36.9 nM (Purdon et al. 2013). In accordance with Dr Rhein's report, the Scottish Health Survey reported that adults of a lower socioeconomic status (low income and/or living in deprived areas) had lower Vitamin D serum concentrations. Additionally the same report suggested that people with a normal BMI had higher blood concentrations than their overweight and obese counterparts. In 2016 the SACN presented data from the latest health surveys for the United Kingdom. In the whole of the UK the average serum concentration of the 65+ group was 47 nM (40.5 nM in winter and 50.5 nM in the summer) but the values were

substantially lower for the institutionalised populations (~30 nM). For Scotland, the SACN reported values slightly higher than what was previously reported, at an average of 41.5 nM.

1.2.3.4 Food sources, dietary intakes and recommendations in Scotland

In 2016 the SACN reported that the minimum protective threshold for Vitamin D serum concentration is 25nM (SACN 2016). To achieve such levels, a daily intake of 10µg (400 IUs) will suffice for 97.5% of the population, even during winter months. However, according to the same report the majority of the Scottish older adults (65+ group) is not likely to achieve such dietary intakes.

In Scotland, from food sources alone, the daily average intake of Vitamin D in the 65+ group is 3.2 µg (men: 3.5 µg, women: 2.9 µg), whereas if the supplements are also taken into account, the intake rises slightly to 4.7 µg (men: 4.7 µg women: 4.6 µg), but remains less than half (47%) of the recommended goal of 10µg day⁻¹ (SACN 2016). The report confirmed the finding of the previous health surveys supporting that obesity, institutionalisation, low income and living in deprived areas can affect negatively vitamin D intake and levels in blood across all adult age groups.

The richest sources of Vitamin D are fish and especially oily fish (e.g. herring, mackerel, salmon, sardines) (5-16µg /100g) and although they are easily accessible in Scotland, they are not the biggest contributor of Vitamin D in the diet of older Scottish adults. The main food sources of Vitamin D in this population cohort are meat and meat products, which contribute 24% to the daily intake. The second important contributor is butter (and spread products) at 19%, whereas fish and

fish products contribute to 16%. Eggs (and egg dishes), cereals (and cereal products) and milk (and dairy products) contribute to 16%, 16% and 4%, respectively.

In conclusion, although there is a trend towards increased serum Vitamin D levels over the last years in older Scottish populations, there is still a great need to educate those at risk (older, obese, of low socioeconomic status and institutionalised) towards achieving higher dietary intakes. In countries with an abundance of food sources rich in Vitamin D, a dietary shift along with mild supplementation protocols should be enough to cover the population needs. Nonetheless, although there is information on intakes of vitamin D in the general population, it is not clear what the intakes of Vitamin D are in older adults with sarcopenic obesity (a similar lack of data exists for protein intakes in the same cohort). The only clear indication so far is that participation in physical activities is low across all groups > 65 years in the UK. Therefore, given the unequivocal evidence for the benefits of exercise training and in older age, lifestyle interventions should incorporate exercise training with higher protein intakes, perhaps alongside vitamin D supplementation, in order to comply with the guidelines and eliminate any confounders resulting from vitamin D deficiencies. What remains to be determined is whether a high protein intake with a controlled caloric intake can be beneficial for those with sarcopenic obesity. The ultimate goals for a lifestyle intervention would be to preserve or increase muscle mass, decrease fat mass, and improve physical function of older adults.

1.3 Aims and objectives

Changes in body composition and strength/ physical function are of utmost importance for older individuals characterised by sarcopenia and obesity. However, a robust method to ameliorate body composition and function has not been established in this population group. Moreover, the prevalence rates of sarcopenia and sarcopenic obesity in Scotland are unknown. The evidence for obesity prevalence is limited to the BMI-derived classifications and not % body fat.

Therefore, the aims of this study intended to address the following research questions:

1. Are there any published scientific trials implementing nutritional and /or exercise protocols to augment body composition and function in older sarcopenic obese older adults, and how effective have they been?
2. How prevalent are sarcopenia, obesity and sarcopenic obesity in Scottish older community dwellers and how do these rates compare with the national average and other countries?
3. Can a weight-loss high-protein diet alongside a complex exercise programme (aerobic, resistance, balance and flexibility) improve body composition and function in older adults with sarcopenic obesity?

Therefore, the first aim of this research was to systematically search, identify and evaluate the effectiveness of nutritional regimens alone or combined with exercise programmes that have been utilised in trials with older community dwellers characterised by sarcopenic obesity. That search sought to find protocols which aimed to augment body composition and/or function in sarcopenic obese older adults.

The second aim was to screen for sarcopenia and obesity in order to assess the prevalence rates of sarcopenia and sarcopenic obesity in community-dwellers aged 65 years and older living in

Lothian, Scotland. The objective was to measure muscle mass, body fat (using both BMI and %BF as obesity criteria) and hand grip strength.

Finally, a novel lifestyle intervention programme combining nutritional modifications and exercise training was designed and delivered to Scottish older adults. The aim of this intervention trial was to assess the impact of nutrition and exercise on body composition and function in older (≥ 65 years) sarcopenic obese community-dwellers. The hypothesis was that an energy-restriction diet with a high protein diet alongside mixed exercise training can significantly affect body composition and strength/function. The primary objective of the intervention study was to assess absolute changes in sarcopenic obesity parameters, particularly changes in 1) skeletal muscle mass 2) body fat and 3) hand-grip strength and physical function. Secondary objectives involved the assessment of 4) health-related quality of life, and 5) changes in the biochemical profile (serum Vitamin D, IGF-1, creatinine, hsCRP, alkaline phosphatase). The final objective was to analyse the dietary habits of those with low muscle mass and high body fat in order to extract some preliminary data on protein intakes and patterns of protein distribution within main meals.

Chapter 2. Effectiveness of nutritional and exercise interventions to improve body composition and strength or function in sarcopenic obese older adults: A systematic review (adapted from the published article)

2.1 Introduction

Sarcopenia has been associated with poor health outcomes such as functional decline, frailty, increased risk of falls, institutionalisation and higher mortality risk (Visser and Schaap 2011). Secondary to functional impairments, muscle atrophy may also contribute to insulin resistance as muscle tissue plays the main role in glucose uptake and utilisation (Gong and Muzumdar 2012; Breen et al. 2013). Obesity is characterised by increased adiposity and is a growing concern due to its progressively rising prevalence rates in older adults (Porter Star et al. 2014). Similar to sarcopenia, obesity can increase the risk of falls and mobility limitations in older age (Houston et al. 2009; Himes et al. 2012), and when used in conjunction with indices of body composition and especially low muscle mass, it can be associated with adverse health effects in older adults such as CVD, metabolic syndrome, type II diabetes and several types of cancer (Oreopoulos et al. 2009). Furthermore, adipose tissue can infiltrate the muscle tissue (Visser et al. 2005) and mediate an inflammatory response (Greenberg and Obin 2006), which can result in muscle atrophy, mobility losses and lower strength and muscle quality (Visser et al. 2002; Visser et al. 2005, Koster et al. 2011).

Sarcopenic obesity is the condition where sarcopenia and obesity occur together (Waters and Baumgartner 2011), however the relationship of the two conditions is far more complex (**Figure 2.1**). According to Baumgartner (2000), a serious concern around increased adipose tissue is that it can mask muscular atrophy, and therefore, the latter cannot be detected unless a specific test on skeletal muscle health is performed. Individuals with sarcopenic obesity are exposed to ~2.5-fold higher risk of reporting Instrumental Activities of Daily Living (IADL)

disabilities compared with adults without obesity but with sarcopenia, or adults with obesity but without sarcopenia (Baumgartner et al. 2004). According to a meta-analysis of 12 prospective cohort studies with a total number of 35,287 participants, sarcopenic obese adults had a 24% higher risk of all-cause mortality compared to their healthy counterparts (Tian and Zu 2016). Therefore, finding ways to stop the deteriorating effects of ageing on body composition and function is of utmost importance for the longevity and quality of life of older adults. Even though sarcopenic obesity has gained significant attention by the scientific community in recent years there is no universally accepted definition, perhaps due to the plethora of definitions and cut-offs for sarcopenia and obesity (Cruz-Jentoft et al. 2010, Prado et al. 2012; Poggiogalle et al. 2014). As an outcome, detection and management of this condition is very challenging for healthcare practitioners.

Despite a growing body of evidence highlighting potentially beneficial nutritional and exercise strategies to reverse or at least attenuate the negative effects of ageing on body composition and physical function (Phillips 2015; McLeod et al. 2016; Witard et al. 2016a) there is still a paucity of studies utilising training and nutritional interventions for older sarcopenic obese participants (Goisser et al. 2015; Poggiogalle et al. 2014). The challenge associated with such strategies lies in the fact that losing body fat while concomitantly gaining or even preserving muscle mass is a very challenging goal. As discussed in Chapter 1, the inherent risk of potential lean mass losses with energy-deficit diets (which could be otherwise a plausible strategy for the young obese and non-sarcopenic adults (Waters et al. 2013)) may negatively impact the musculoskeletal health of older sarcopenic individuals (Weinheimer et al. 2010; Shah et al. 2011; Armamento-Villareal et al. 2012; Waters et al. 2013). Thus, it appears that most intervention trials have aimed to attenuate muscle loss at an early stage rather than try to ‘reverse’ an established condition related to advanced ageing such as sarcopenia or sarcopenic obesity, which would be far more challenging (Phillips 2017).

Pharmacological approaches are currently limited to androgens and oestrogen administration and whilst they can potentially promote positive changes in body composition and function, the benefit to risk ratio may not be favourable for this population group (Calof et al. 2005; Horstman et al. 2012). While exercise training may be beneficial for both obesity and sarcopenia, the dietary management of obesity may require energy restriction, whilst management of sarcopenia requires an increased intake of macronutrients, especially protein (Naseeb and Volpe 2017). However, as previous systematic reviews have reported (Weinheimer et al. 2010; Stewart et al. 2014), although exercise interventions have the potential to attenuate the loss of muscle mass in older age, cases where lean mass and muscle mass have decreased after an exercise or physical activity programme are not uncommon. Therefore, exercise interventions need to be carefully tailored to sarcopenic obese individuals so that the frequency, intensity and volume are adequate enough to produce a meaningful change in body composition and physical function, but without compromising musculoskeletal health.

To date, there has been no systematic review assessing the effectiveness of nutritional and exercise strategies, alone or combined, to improve body composition and strength or function in sarcopenic obese older individuals. Therefore, the purpose of this systematic review was to assess the effectiveness of diets modulating the nutritional content (especially energy and protein or amino acids), exercise training regimens, or diet and exercise training combined, in older adults with sarcopenic obesity.

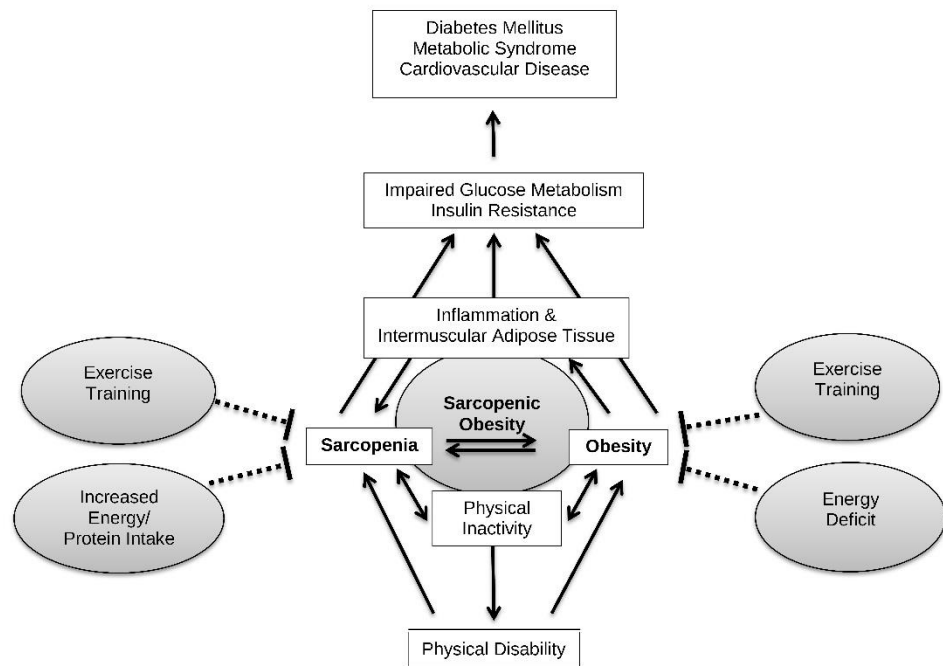


Figure 2.1 Relationship between sarcopenia and obesity and associated risks as well as management strategies. Notes: Solid arrow: direct and positive association; Dashed line management strategy attenuating/reversing the condition:

2.1.1 Aims

The focus of this systematic review was to determine the effectiveness of protein or energy-modulating regimens, with or without exercise training on body composition and function in adults, 65 years of age and older with sarcopenic obesity. In particular, the primary aims were to 1) determine changes in absolute muscle mass, total appendicular skeletal muscle (TASM), skeletal muscle index (SMI), fat mass, % body fat, body weight and body mass index (BMI) and 2) assess changes in muscle strength and/or physical function (including muscle strength, power, gait speed and balance). The secondary aim was to evaluate the effect of these

interventions on quality of life, metabolic profile, activities of daily living, adverse effects of supplementation or food choices, compliance rates and changes in habitual dietary intake during or after the interventions.

2.2 Methods

This systematic review was performed according to the Preferred Reporting for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The protocol was registered with the International prospective register of systematic reviews (PROSPERO registration number: CRD42015017311).

2.2.1 Search Strategy

The Cochrane Central Register of Controlled Trials, MEDLINE (via EBSCOhost Research Databases), CINAHL and SPORTDiscus were searched up to and including May 2016. The last search was conducted on 22 May 2016. No limits were applied for date of publication. Combinations of key terms with Medical Subject Headings (MeSH) and Boolean operators were used. The main keywords and terms used were: Age*/ Adult*/ Old*/ Elderly/ Senior, Sarcopeni*/ Lean/ Frail/ Atrophy/ Weakness, Obes*/ Overweight/ Body Mass Index, Exercise/ Training/ Strength/ Muscle/ Mass/ Hypertrophy/ Size/ Body Composition, Diet/ Supplements/ Protein/ Amino Acids/ Energy, Life Quality/ Intervention. The search limiters were English language and studies with human participants (the complete search strategy is presented in Appendix 2).

2.2.2 Inclusion Criteria

Randomised control trials (RCTs), randomised control crossover trials and controlled clinical trials were included, using prospective nutritional and/or exercise interventions to attenuate/reverse the loss of muscle mass, reduce adipose tissue and optimise muscle strength or function. Given that there is no universally accepted definition for sarcopenia, some authors may have used different terms to define the participants, e.g. 'lean', 'weak' or 'frail'. Such studies were included only if the participants could be characterised as sarcopenic based on the definition criteria and cut-off scores as presented by the EWGSOP (Cruz-Jentoft et al. 2010). Therefore, studies were included only if they presented data for a) body composition (data on absolute muscle mass, appendicular muscle mass, Total Appendicular Skeletal Muscle (TASM) or Skeletal Muscle Index (SMI) assessed by Dual-energy X-ray Absorptiometry (DXA), Bioelectrical Impedance Analysis (BIA), Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI) and b) muscular strength and/ or physical function identified by one of the following tests: handgrip strength, knee flexion/extension, peak expiratory flow, gait speed, the Short Physical Performance Battery test (SPPB), the timed up-and-go test or the stair climb power test. The mean age cut-off for inclusion was ≥ 65 years based on how 'old age' is defined in the joint recommendations from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) (Nelson et al. 2007). The inclusion criterion for obesity was defined as body fat percentage (BF%) $\geq 28\%$ in men and $\geq 40\%$ in women (Baumgartner et al. 2004) or in the absence of %BF data, a BMI $\geq 27 \text{ kg m}^{-2}$. For any given BMI, a sarcopenic person will have by definition more body fat compared with their non-sarcopenic counterparts, therefore, adults with sarcopenia can present high-adiposity at BMIs substantially lower than 30 kg m^{-2} (Newman et al. 2003a). Moreover, it is not uncommon for intervention studies to recruit overweight and obese participants with a BMI $\geq 27 \text{ kg m}^{-2}$ especially when the focus is on sarcopenic obesity (Prado et al. 2012; Donini et al. 2013; Poggogalle et al. 2014). Studies which presented neither the % body fat nor BMI

were included only if these indices could be derived from the weight, height and body fat mass values or if the authors of the study when contacted provided the essential information.

Nutritional interventions aiming to promote muscle hypertrophy by macronutrient profile modification or weight loss via energy restriction were of primary interest. Studies providing extra macronutrients (especially proteins or amino acids and their metabolites) or micronutrients either in the form of whole foods or dietary supplements administered through the oral route only, were considered. Exercise regimens including resistance, balance, aerobic and mixed exercise protocols influencing lean mass, fat mass, muscle hypertrophy, strength, power, speed and/ or physical functional were of primary interest.

2.2.3 Exclusion Criteria

Studies were excluded if the protocol involved administration of any kind of prescription only/pharmaceutical agents or any type of supplementation administered via a route other than oral. Studies including participants with cachexia or with serious mental and cognitive conditions prohibiting adherence to a structured exercise/ nutrition regime such as Alzheimer's or dementia, were excluded.

2.2.4 Study Selection

The titles and abstracts were screened for eligibility and the full text copies of potentially eligible articles were obtained for further inspection. The full-text articles were independently assessed for eligibility by two reviewers. The reference lists of eligible articles and review papers as well as journals specialising in geriatrics were hand searched for potential articles. Any disagreement between the two reviewers was resolved by a third reviewer.

2.2.5 Data Extraction

Data were extracted from each eligible article using a standardized form by two reviewers. Any disagreements between the two reviewers were resolved by discussion until consensus was reached. Demographic (age, gender, ethnicity/host country and habitation), methodological (study design, sample sizes, duration, nutritional/dietary and/or exercise intervention plan, supplement type, dosing/frequency of administration, exercise training type/frequency/volume, assessment method, blinding) and outcome data (changes within and between groups, significance, drop out rates, compliance, adverse effects) were compiled in a standardised Excel spreadsheet.

2.2.6 Quality Assessment

The quality of the studies was assessed by two independent reviewers using a modified version of the Downs and Black rating scale (Downs and Black 1998; Eng et al. 2007). The Downs and Black scale is one of the most credible instruments for the quality assessment of randomised (Olivo et al. 2008) and non-randomised intervention trials (Saunders et al. 2003). Modified scoring for Question 27 was performed as detailed by Eng et al. (2007): the original scale had a maximum score of 32 but in this review Question 27 was modified to score either 0 or 1 point instead of the original 0-5 points. Therefore, the maximum total score for the five sections of the scale (reporting, external validity, internal validity/bias, internal validity/confounding, power) was 28.

2.2.7 Principal Summary Measures

The primary outcome measures were 1) differences in mean of skeletal muscle mass (either absolute, relative or appendicular) and body fat or BMI, and 2) differences in mean of muscle strength and physical function/performance.

2.3 Results

2.3.1 Description of studies

Our search strategy resulted in 1,440 potential articles. After the exclusion of 1,331 articles based on titles and abstracts, 109 full-text articles reporting 109 studies were retrieved and assessed for eligibility. The detailed flow chart of the selection process is presented in **Figure 2.2**. The authors of two potentially eligible studies (Wouters-Wesseling et al. 2003; Kwon et al. 2015b) were contacted for further information but retrieval of all the essential data was not possible for reasons unrelated to this review, therefore the articles were excluded. A total of $n=2$ studies (study A by Aleman-Mateo et al. 2012 and study B by Balachandran et al. 2014) including $n=61$ participants met the inclusion criteria and were included in the review. Study A was a nutritional intervention and study B an exercise training intervention; neither of the studies combined exercise with diet.

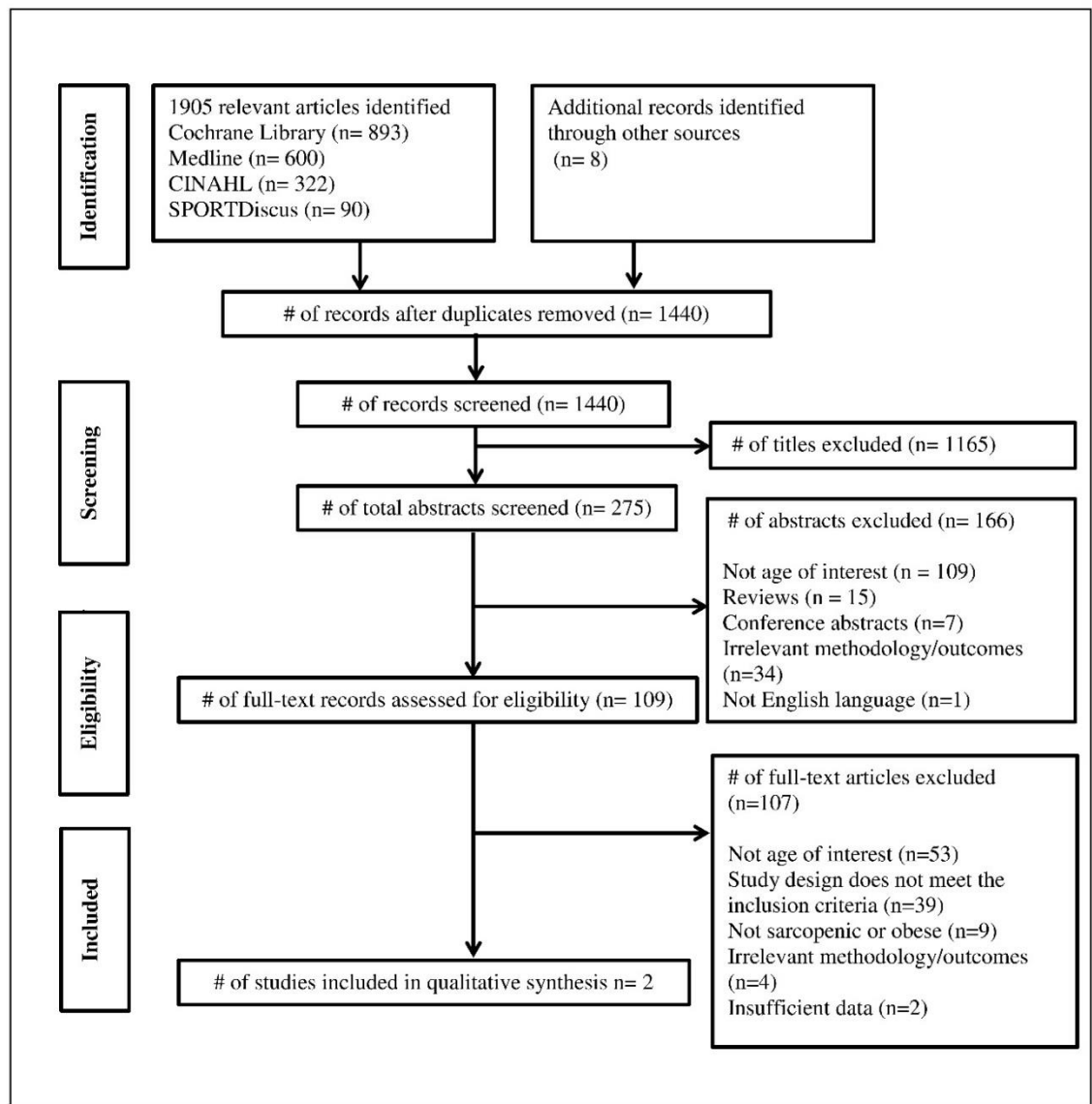


Figure 2.2 Information flow through the phases of the systematic review according to PRISMA guidelines.

2.3.2 Quality Assessment

The two studies were randomised control trials of moderate methodological quality based on the modified Downs and Black rating scale (Downs and Black 1998; Eng et al. 2007). The total score for each study was 18 out of 28. The summary key information of the two methodological strengths and limitations is presented in

Table 2.1. The complete breakdown of the scoring in the different subsections of the scale is shown in **Table 2.2**. Both studies performed power calculations to determine the population sample size prior to recruitment but finally study B (Balachandran et al. 2014) was underpowered; target was $n=21$ per group but the final analysis was conducted with $n=9$ and $n=8$ for the control and intervention group, respectively. In study A only the testers were blinded but not the participants. In study B the two groups were exercising at different times, therefore participants were partially blinded. Study A reported and tested for a range of potential confounders but failed to report essential information regarding the participants' dietary intake at baseline and follow-up. The results in Study A were based on an intention-to-treat analysis whereas in Study B the analysis conducted was per-protocol.

Table 2.1 Summary key points of the included study designs.

Study	Summary	Strengths	Limitations
Study A (Aleman-Mateo et al. 2012) Nutritional Intervention	-40 participants -3 months -Habitual diet plus 210g Ricotta cheese ·day ⁻¹ (intervention) vs habitual diet (control)	-Intention to treat analysis -Body composition by dual-energy xray absorptiometry -Physically-independent participants. -Baseline and follow up clinical tests for kidney and liver function -Blinded personnel delivering the assessment tests.	-Lack of baseline and follow up dietary intake and physical activity data (unclear whether they were not assessed or not).
Study B (Balachandran et al. 2014) Exercise Intervention	-21 participants -15 weeks -High speed circuit resistance (HSC) training (Intervention) vs strength hypertrophy (SH) resistance training (control)	-Independent living community-dwellers. -Participants were partially blinded to the intervention. -Testing personnel blinded -All sessions supervised by 2 physiology majors	-No allocation concealment -Per-protocol analysis - Underpowered -Characteristics of participants lost to follow-up not described -No description of the exercise setting

Table 2.2 Assessment of the methodological quality of the included studies with the modified Downs and Black Scale.

	Reporting (/11)	External Validity (/3)	Internal Validity Bias (/7)	Internal Validity- Confounding (/6)	Power (/1)	Total (/28)
Study A (Aleman-Mateo et al. 2012)	9	1	4	3	1	18
Study B (Balachandran et al. 2014)	8	0	7	2	1	18

2.3.3 Participant Characteristics

Participants in study A (Aleman-Mateo et al. 2012) were physically-independent individuals living in Mexico. Their mean \pm SD age was 76 ± 5.4 years. The mean percentage body fat of men and women in the intervention group was 31.3% and 45.6%, respectively, while in the control group the respective values were 32.4% and 45.7%. The mean BMI and TASM were $26.3 \pm 3.8 \text{ kg m}^{-2}$ and $15.5 \pm 2.9 \text{ kg}$, respectively. Out of the 40 participants (17 men and 33 women) 29 completed the protocol.

All participants in study B (Balachandran et al. 2014) were independent-living community dwellers from South Miami (USA). The mean \pm SD age and BMI of participants was 71.3 ± 7.8 years and $32.6 \pm 4.7 \text{ kg m}^{-2}$, respectively. Their mean SMI was $6.6 \pm 1.0 \text{ kg m}^{-2}$. Of the 21 initial participants, 17 completed the protocol, 16 of whom were female.

2.3.4 Study Design

The aim of study A (Aleman-Mateo et al. 2012) was to assess whether the addition of a protein rich food to the habitual diet could increase TASM and strength in older sarcopenic individuals. The study was a 3-month RCT with a control (habitual diet) and an intervention group (habitual diet + 210g ricotta cheese per day; RCH+HD). The cheese provided 15.7g extra protein (including 8.6 g of EAAs), 10.4 g of carbohydrate, 18.4 g fat and a total of 267 kcal per day. Cheese was divided into three 70 g portions that were pre-packed and delivered ready-for-consumption to the participants, who were instructed to consume the cheese portions along with their usual breakfast, lunch and dinner. Dual-energy x-ray absorptiometry was used to measure TASM and body composition changes.

Study B (Balachandran et al. 2014) was a 15-week single blind RCT which aimed to assess the effectiveness of a novel exercise regime based on a high speed circuit (HSC) resistance

training programme (intervention) on body composition, neuromuscular performance and IADL compared with a conventional strength hypertrophy (SH) regime (control group) in sarcopenic obese community-dwellers. Body composition was assessed by single frequency BIA. Both groups performed exercises at 11 pneumatic gym machines (five lower and six upper-body) twice per week. The SH protocol involved three sets of 10-12 repetitions at 70% of the 1RM with a 1-2min recovery break between sets. Participants were instructed to keep a similar speed of contraction for the concentric and eccentric phase (2 sec). Resistance increased by five percent only when the participant could perform three sets of 12 repetitions. The HSC group performed 10-12 repetitions at all 11 exercises in a circuit pattern (i.e. moving from one exercise to the other) with no break in between exercises unless one full circuit was complete. Then they were allowed a 1-2 min recovery break and were asked to repeat the same circuit until they had completed three full circuits. The resistance load was selected based on the maximum power output for each machine and ranged from 50 to 80 percent 1RM. The concentric phase was performed as fast as possible while the eccentric in 2 sec. Resistance load was increased by five percent when a power plateau was reached. A typical HSC and SH training session would last 40-45 min and 55-60 min, respectively. No dietary or nutritional element was introduced in the study and neither dietary patterns nor intakes were reported.

2.3.5 Outcomes

Body composition

No significant changes were seen in body composition in either experimental or control groups. In study A (Aleman-Mateo et al. 2012) the addition of ricotta cheese resulted in no significant changes in lean mass, TASM or body fat in the intervention group or control group (**Table 2.3**). Secondary analysis by gender showed that although men ($n=8$) in the intervention group experienced an increase in TASM by 490g, this was not significantly different either from baseline or when compared against the control group ($p=0.42$), which gained a non-

significant 220g of TASM. Similarly, in study B (Balachandran et al. 2014) no statistically significant differences were detected in any of the body composition indices, regardless of the exercise regimen (**Table 2.3**). Skeletal muscle index (SMI) increased non-significantly in both groups (from $6.5 \pm 0.66 \text{ kg} \cdot \text{m}^{-2}$ to $6.6 \pm 0.59 \text{ kg} \cdot \text{m}^{-2}$ in HSC and from $6.7 \pm 0.45 \text{ kg} \cdot \text{m}^{-2}$ to $6.8 \pm 0.42 \text{ kg} \cdot \text{m}^{-2}$ in SH).

Strength and/ or function

In study A (Aleman-Mateo et al. 2012), the group receiving the extra protein had a non-significant increase in strength (+0.9% relative increase). Although the control group experienced a drop in strength (-3.5%), the difference between the two groups did not achieve statistical significance ($p=0.06$).

Study B (Balanchandran et al. 2014) reported significant improvements in several aspects of strength and function in both exercise groups (**Table 2.3**). In particular, the strength-hypertrophy (SH) control group experienced significant improvements in leg press 1RM by 22% ($p<0.01$), chest press 1RM by 16% ($p=0.03$), leg press peak power by 19% ($p=0.03$) and chest press peak power by 15% ($p<0.01$) whereas a non-significant increase of 12% was detected in hand grip strength (from $17.3 \pm 2.7 \text{ kg}$ to $19.4 \pm 4.6 \text{ kg}$; $p>0.05$). The HSC group had a significant improvement in chest press 1RM by 21% ($p<0.01$), leg press peak power by 41% ($p<0.01$) chest press peak power by 24% ($p<0.01$) but hand grip strength did not change significantly (increased by 10%, from $17.7 \pm 7.8 \text{ kg}$ to $19.4 \pm 6.6 \text{ kg}$; $p>0.5$). Between group differences were detected only for leg press peak power, with the HSC group performing better than the control by 158 W (95% CI (2, 315), $p=0.005$).

The SPPB test improved significantly over time only within the HSC group from 8.0 ± 1.5 to 9.6 ± 1.2 ($p=0.02$). Between group differences favoured the HSC group [mean difference 1.1 (95% CI (-0.1, 2.4), $p=0.08$)] although this was not statistically significant.

Secondary Outcomes

Consumption of ricotta cheese in study A, resulted in significantly lower fasting insulin levels in men ($p=0.05$) but not in women. There were no other significant changes in hepatic markers (SGOT, SGPT and Alkaline Phosphatase), kidney function (blood urea, uric acid, creatinine and GFR), anabolism (IGF-1) or insulin resistance. No cases of microalbuminuria were present in the RCH+HD group after the intervention period. Moreover, 25% of women in the intervention group reported early satiation after the consumption of ricotta cheese, however dietary intakes were not reported. Eight participants from the intervention group dropped out; five were due to personal health issues, two could not eat the entire portion of ricotta cheese and one had to relocate. In the control group three people dropped out (two for personal reasons and one for modifying the habitual diet). However, all participants were measured pre- and post-intervention according to an intention-to-treat analysis.

The exercise intervention in study B resulted in acute joint pain only in the SH group. In addition, the HSC group reported significantly lower rates of perceived exertion (RPE) with a mean difference of -1.5 (95% CI -2.0, -0.12, $p=0.04$). Adherence rates were similar in the two groups; 81% in HSC and 85% in SH. Regarding the Instrumental Activities of Daily Living (IADL) there were significant improvements within both groups (pre vs post); namely, time needed for jacket on and off (from 11.5 ± 3.5 s to 10.2 ± 2.0 s; $p=0.04$), scarf pick-up (5.2 ± 1.1 s to 4.7 ± 0.9 s; $p<0.01$) and pan carry (4.9 ± 0.6 s to 3.9 ± 0.7 s; $p<0.01$) improved significantly within the control group, while the HSC group experienced significant improvements in time

for sit-to-stand (from 16.1 ± 5.7 s to 13.4 ± 3.9 s; $p=0.02$) and pan carry (5.4 ± 1.3 s to 4.5 ± 1.2 s; $p<0.01$). No differences were observed between the two groups in the aforementioned IADLs.

In summary, neither of the studies had a significant effect on body composition in sarcopenic obese older adults. The introduction of ricotta cheese in the habitual diet of participants in study A aimed to increase their protein intake but it was not reported whether or not this was achieved, nor to what extent. In the same study, there was a trend for increase in strength in the intervention group but not significantly. The only significant improvement reported was the fasting insulin level but only in men in the intervention group. Despite the lack of body composition changes, in study B, the high speed circuit resistance training and strength hypertrophy resistance training protocols significantly improved strength, power and function indices but did not significantly change either muscle mass or body fat in any of the groups.

Table 2.3 Summary of the included studies

Study	Setting/ Study Design/ Duration	Group	Participants Mean Age (SD)/ characteristics	Exercise Training	Nutritional Intervention	Sample Size (n) Drop-out (DO n) Female (F n) Adherence (%)	Assessment of a)body composition b) strength or function	Outcome Measure
Study A (Aleman- Mateo et al. 2012)	Mexico/ RCT: two arms, one control, one intervention / 3 months	Control	76.7 (5.8) / physically- independent, sarcopenic based on low TASM and strength, obese based on %BF	No	Habitual diet (HD)	Baseline n=20 Final n= 12 DO n= 8 F n=12 N/A	a)DXA b) HG strength	TASM →, FM →, LM →, HG →
		Intervention	75.4 (5.0)/ independent living sarcopenic based on low TASM and strength, obese based on %BF	No	HD plus 210 g of ricotta cheese/day, (providing 15.7 gr extra protein/day)	Baseline n=20 Final n=17 DO n=3 F n=11 N/A		TASM →, FM → , LM →, HG →
Study B (Balachandran et al. 2014)	USA/ RCT: Two arms, one control, one intervention/ 15 weeks	Control	71 (8.2)/ independent living community dwellers from South Miami, sarcopenic based on SMI and strength, obese based on %BF and BMI	strength- hypertrophy (SH) training, 11 exercises, 3 sets of 10-12 reps per set at 70% 1RM	No	Baseline n=10 Final n=9 DO n= 1 F n=8 85%	a)BIA b) HG strength, SPPB, Leg press 1RM, Chest press 1RM, Leg press power, Chest press power,	SMI→, %BF →, SPPB→, Leg 1RM↑**, Leg Power↑*, Chest 1RM↑*, Chest Power↑**, HG→
		Intervention	71.6 (7.8)/ independent living community dwellers from South Miami	High speed circuit (HSC) training, 11 exercises: 3 circuits of 10-12 reps per exercise at loads that maximised peak power output	No	Baseline n=11 Final n= 8 DO n= 3 F n =8 81%		SMI→, %BF →, SPPB↓*, Leg 1RM →, Leg Power↑**‡, Chest 1RM↑**, Chest power↑**, HG→

Notes: → no significant change, ↑significant increase, ↓significant decrease, * <0.05 , ** <0.01 , † significantly better than the control group;
%BF, percent body fat; BMI, body mass index; DXA, dual-energy xray absorptiometry; FM, fat mass; HG, handgrip; LM, lean mass; RCT, randomised control
Trial; RM, repetition maximum; SPPB, short physical performance battery test; TASM, total appendicular skeletal muscle.

2.4 Discussion

The aim of this review was to assess the effectiveness of nutritional and/or exercise interventions on body composition and strength or function in older sarcopenic obese adults. With regard to the main outcomes, neither an increase in protein intake by $15 \text{ g} \cdot \text{day}^{-1}$ nor a resistance exercise protocol produced significant improvements in body composition indices in older sarcopenic obese adults. However, the exercise intervention (both the control group following a strength-hypertrophy resistance exercise protocol and the intervention group utilising a high-speed power-orientated circuit resistance training) reported significant improvements in both strength and function. However, the small number of studies identified clearly highlights the need for more research in the area and potentially a consensus for the definition of sarcopenic obesity.

Study A (Aleman-Mateo et al. 2012) attempted to utilize the effectiveness of protein in enhancing skeletal muscle mass accretion rates. Although the authors (Aleman-Mateo et al. 2012) acknowledged that the suggested recommendations for protein intake in the older sarcopenic individuals are $1.2\text{-}1.5 \text{ g} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$ they did not report the daily protein intake which was a major limitation. It has been suggested that maximal muscle protein synthesis (MPS) rates in older adults can be achieved using $\sim 35 - 40 \text{ g protein} \cdot \text{meal}^{-1}$ (Pennings et al. 2012; Yang et al. 2012; Moore et al. 2015) or $0.4 \text{ g protein} \cdot \text{kg bw}^{-1} \cdot \text{meal}^{-1}$ (Moore et al. 2015). A valid question would be whether a daily addition of 210 g ricotta cheese (delivering 15.7g protein) to the habitual diet could practically augment muscle mass in sarcopenic older adults. It is important to note that the cheese servings were not consumed in one meal but were spread over the three main meals, that is, 70 g cheese ($\sim 5 \text{ g}$ of extra protein) consumed across breakfast, lunch and dinner. Protein intakes in Study A were not reported but extrapolation of the data from studies in similar population cohorts (Tieland et al. 2012b), suggests that older individuals are not likely to consume an

adequate amount of protein during all main meals. Tieland et al. (2012b) reported mean protein intakes of ~8g, ~18g and ~29g for breakfast, lunch and dinner, respectively. Therefore, it is uncertain whether the addition of 5g protein in the main meals in study A was enough to significantly augment MPS. Another confounder may have been the potential impact of the addition of cheese on the habitual diet given the fact that 25% of women in Study A experienced early satiation. It could be consequently speculated that women's habitual diet was modified with the addition of ricotta, potentially displacing the intake of other foods. However this cannot be confirmed as the habitual diet was not reported.

In study A, even though there was a trend towards increased strength, it could be argued that higher, and perhaps different distributions of protein intake were needed to enhance muscle strength and accretion of skeletal muscle mass. The potential for high protein meals to maintain or increase muscle mass and strength in older adults has been recently reported by Loenneke et al. (2016) who reported that one or two meals containing 30-45 g protein · day⁻¹ were associated with higher lean mass and strength compared with those who did not consume any meals over the threshold of 30 g protein. It should be also noted that the power calculation for sample size in study A was based on lean mass as a primary outcome, rather than muscle strength. Therefore, it is unknown whether a larger sample size was needed to reveal a significant change in handgrip strength.

In spite of possible methodological limitations of study B the improvements in strength, power and IADL provide evidence to support that exercise can improve several domains of physical performance such as strength and power. This is in agreement with previous reviews supporting the benefits of resistance exercise training on clinically important outcomes even in the absence of increased muscle mass (Cruz-Jentoft et al. 2014; Churchward-Venne et al. 2015; Witard et al.

2016a). This may be partly accounted for by the adaptive plasticity in the neuromuscular system and skeletal muscle tissue in response to resistance exercise even in advanced older age (Aagaard et al. 2010). A significant improvement particularly in power, can be very important for sarcopenic obese individuals since muscle power can be a predictor of mobility skills and a more influential indicator of physical capacity compared with absolute changes in strength (Bean et al. 2003). Another interesting finding from study B was the large effect size observed in peak leg power achieved by exercising at 50% 1RM. To a certain extent, that finding may be explained by the novel aspect of the study design, that is, the resistance exercise progression protocol. Resistance load would increase only when a power plateau was reached (Balachandran et al. 2014). Therefore, the protocol was designed in such a way as to favour maximum power output and possibly this fact may explain the lack of significant changes in leg strength in the HSC group but significantly better improvements in leg power compared with the control group.

With regards to the lack of significant changes in lean mass or muscle mass after exercise training in sarcopenic adults, it has been reported elsewhere in the literature (Cruz-Jentoft et al. 2014) and may be accounted for by protocol-specific differences such as duration, type, intensity, time-under-tension, volume and frequency of exercise as well as the quality and availability of adequate nutrients (protein/amino acids) to elicit a muscle anabolic response and consequently hypertrophy (Borde et al. 2015; Witard et al. 2016a; Witard et al. 2016b). One limitation of study B (Balachandran et al. 2014) was the lack of control for dietary intake which could have partly explained the lack of effect on body composition. It has been shown that a bout of resistance exercise can stimulate muscle protein synthesis (MPS) to a higher degree than protein breakdown, however, in the absence of post-workout provision of nutrients (especially protein) it can result in negative net muscle protein balance (Philips et al. 1997; Koopman and Van Loon 2009) and is a limitation of study designs to date.

These data support the potential benefit of a resistance exercise programme within lifestyle intervention protocols due to its positive effect on muscle strength, power and function in sarcopenic obese older adults. Although no statistically significant body-composition changes were reported in the included studies, the significant improvements in strength, power and function may be more important for the quality of life of older sarcopenic obese adults than absolute changes in body fat or lean mass *per se*. In the protein study (study A), even though there was a trend towards a maintenance of muscle strength, it could be argued that higher protein intakes and potentially a more careful timing/distribution of protein were needed to enhance muscle strength and accretion of skeletal muscle mass.

More intervention trials should be undertaken to identify effective lifestyle strategies in adults with sarcopenic obesity that will inform more robust approaches to combat this condition. Future research should also bridge the gap in knowledge with respect to multimodal approaches combining resistance exercise training with dietary strategies. More trials combining resistance exercise training with protein supplementation, in order to augment muscle mass and strength, and potentially alongside an energy-deficit diet to promote fat loss are needed. According to a recent study in young adults, after a whole-body resistance exercise the body is able to utilize 40 g protein for anabolic purposes (Macnaughton et al. 2016). Therefore, considering that older adults require more protein than their younger counterparts to reach the same MPS rates, it should be corroborated in future studies whether the optimal protein dose is even higher than 40 g in older adults performing whole-body resistance exercise workouts. It is also important to note that although the need to augment/preserve muscle mass is paramount, a reduction in fat mass and especially fat infiltrating the muscle tissue is equally important, since intermuscular fat can lead to mobility limitations (Visser et al. 2005). Exercise training can preferentially reduce

intermuscular adipose tissue more effectively than caloric-restriction alone (Murphy et al. 2012). However, a combination of exercise with caloric-restriction can lead to greater losses of total fat mass, which in turn may result in greater improvements in physical function, sometimes even at the expense of lean tissue (Villareal et al. 2011a; Beavers et al. 2014).

2.4.1 Limitations

The main limitation of this review is the scarcity of studies with older population groups and the strict inclusion/exclusion criteria implemented by the Reviewers. Only studies including obese older adults having the sarcopenic phenotype as defined by the EWGSOP (Cruz-Jentoft et al. 2010) using an appropriate methodology to assess body composition, were reviewed. Although in 2010 the EWGSOP agreed on the definition and assessment of sarcopenia adopting criteria for low muscle and low strength or function, it is not uncommon for studies (Mason et al. 2013; Maltais et al. 2016) to use only the criterion of low muscle mass to define sarcopenia as it was initially proposed (Evans 1995). Such studies were not included in the current review. In addition, two studies conducted before 2010 were excluded. In one study, muscle mass was assessed using urinary creatinine (Yarasheski et al. 1999), a method not included in the EWGSOP definition, and in the second study (Wouters-Wesseling et al. 2003) despite using an acceptable methodology the authors could not provide the required information (skeletal muscle mass pre- and post-intervention) in order to confirm eligibility. Similarly, a recent study (Kwon et al. 2015b) with Asian older and possibly sarcopenic individuals was excluded due to lack of essential data on body fat and BMI, and after personal communication, retrieval of that information was not possible.

Although of vital importance, there is an apparent lack of interventions with sarcopenic obese older adults. This is in accordance with Finger et al. (2015) who commented that interventions may refer to or discuss sarcopenia, however, the number of studies recruiting sarcopenic adults is

very limited. Indeed, there is a number of reviews (Weinheimer et al. 2010; Li and Heber 2011; Cermak et al. 2012; Malafarina et al. 2012; Poggiogalle et al. 2014; Goisser et al. 2015) presenting intervention studies with healthy, overweight, obese or sarcopenic older participants which usually extrapolate data in order to propose ways to improve the sarcopenic obesity phenotype in older age.

2.4.2 Conclusion

This review assessed studies investigating the effectiveness of exercise or nutritional interventions to improve the body composition and strength/function of older adults with sarcopenia and obesity. None of the included studies significantly reduced body fat or increased either skeletal muscle mass or lean mass. Although the number of included studies was low, it is evident that an exercise intervention can elicit significant improvements in aspects of physical function such as muscle strength, power and ability to perform activities of daily living. The addition of 15 g protein·day⁻¹ to the habitual diet via cheese consumption revealed a non-statistically significant trend towards increased handgrip strength, and resulted in an improved insulin response in men but not women. The lack of published data highlights the necessity for new research adopting universally accepted cut-offs for sarcopenic obesity with the inclusion of appropriately designed exercise programmes and dietary regimens, and with detailed assessments of dietary patterns and intakes for the targeted population group.

Chapter 3. Protocol development for a lifestyle intervention for older sarcopenic obese community-dwellers: Rationale for a high-protein hypocaloric diet combined with mixed exercise training.

3.1 Overview

Chapter 1 presented the evidence supporting the beneficial effects of exercise and high-protein nutritional regimens, however, the systematic review in Chapter 2 highlighted that such protocols have not been employed in sarcopenic obesity. Thus, protocols for sarcopenic obese older community-dwellers are currently lacking and in particular, there is a lack of practical and realistic interventions that combine exercise with an appropriate nutritional regimen. Therefore, this Chapter presents a) the evidence for the proposed lifestyle intervention that has been employed in the current study, and b) discusses its practicality and how it can be implemented and monitored. Thus, in the first section of this chapter (*section 3.1*) a justification for the proposed protocol is presented along with the operational implications. In the second section (*3.2*), an overview is provided of the different methodologies allowing researchers to assess the effectiveness of the intervention.

3.1.1 Exercise

Before designing an exercise intervention that can be replicated at a community level, it is essential for researchers to take into consideration the specific characteristics, abilities and preferences of the population group that is being targeted. When it comes to older adults participating in exercise programmes, in order for them to adopt and maintain a regular attendance, the programme must be inexpensive, realistic and enjoyable (Jette et al. 1999). It is especially important in adults with obesity to select the right exercise equipment in order to ensure adherence to the programme (Baechle and Westcott 2010). Moreover, the exercise routine needs to be challenging enough to

elicit physiological adaptations but at the same time manageable, realistic and not overly complicated to perform, in order to avoid discouraging the trainees and undermine their self-esteem, which can eventually result in diminished interest (Chen et al. 2013). Therefore, before even initiating the design of the exercise-specific principles such as frequency, intensity, type of exercise and duration, the aim of the current strategy was to create a programme that will be appropriate for a group of older adults with varying levels of physical skills and capacity to exercise. Equally vital is the fact that the programme needs to be easily replicated and maintained at a community setting without the need for sophisticated or expensive equipment.

It is often reported that obese older adults prefer exercises and machines that can accommodate their weight and capacity for physical movements (Baechle and Westcott 2010). When balance is a concern the ideal way to initiate an exercise programme is by adopting a stable position (ideally seated) as a starting point and observe the trainee's performance in order to provide feedback and support as necessary. Moreover body-weight exercises are a good starting point for someone who does not have experience in performing a complex exercise routine (Baechle and Westcott 2010). Therefore using chair-based exercises combines all previous principles and additionally, removes the burden of having participants adopt unfamiliar positions when using fixed-path machines. Additionally, obese or not highly functional trainees feel more comfortable, at least at the initial stages of a programme, when performing activities in a supported environment/piece of equipment instead of a treadmill or outdoor jogging (Baechle and Westcott 2010).

As presented in section 1.2.1.3, the UK Department of Health (2011) and the ACSM (2014) recommend 150-300 mins of a moderate intensity multi-modal exercise training (i.e. a programme combining strength, aerobic, balance and stretching exercises) for older adults (ACSM 2014). The aim of combining different training modalities is to promote improvements in several aspects of

physical fitness such as strength, power, muscular and cardiovascular endurance, flexibility and balance. High body functionality is essential considering that neuromuscular coordination, proprioception, stability and balance are crucial for older adults and especially for those with increased risk for physical disabilities. A regular mixed exercise programme (3 x 90 min weekly sessions for three months combining balance, flexibility, aerobic and strength exercises) can help older frail and obese adults to augment their strength and appendicular lean mass (Villareal et al. 2011b). The resistance protocol in this study involved exercising at progressively increasing intensities (from 65 to 80% 1RM) on a Hoist machine and a squat rack. Moreover, at the end of the 3-month intervention the mixed MPS rates significantly increased by approximately 50%. However, there was no interaction between training and protein feeding-induced changes in MPS over time, since Δ MPS (post-prandial – basal) rates between pre-intervention and post-intervention were similar, at $\sim 0.02\%/h$. This lack of effect in response to feeding after 3-months of exercise training may be accounted for by the low protein content of the supplement used (~ 11 g mix of milk and soy protein), which was possibly too low to significantly stimulate MPS in older adults, and capture any changes in anabolic sensitivity in response to exercise and protein feeding.

Although progressive resistance training using free-weights (e.g. dumbbells, barbells, medicine balls etc.) and/or fixed path machines have a well documented positive impact on muscle mass, strength, power and function (Liu and Latham 2009; Peterson et al. 2010; Steib et al. 2010; Villareal et al. 2011b), their use may not be ideal for this cohort since they may not be easily accessible (Martins et al. 2013). Moreover, it is not ideal for a community-based intervention, where the organisers may not be able to afford to provide such equipment due to financial or practical limitations (e.g. lack of space, inability to transport). An alternative to machines and free weights is the use of elastic bands (EBs) that come in different levels of resistance. The main advantage of the EBs is the fact that they can be used anywhere since they are portable,

inexpensive and easy to use and maintain (Colado and Triplett 2008). In addition, elastic bands can work in multiple planes, unlike free weights which work only against gravity. For example to perform a chest press with free weights one will need to adopt the supine position and move the weights vertically upwards (against gravity) to engage the chest muscles. Elastic bands on the other hand can be used while seated or standing which is more convenient especially for the older adults who are in the initial stages of an exercise programme.

The main purported disadvantage of EBs comes from its key mechanical characteristic, that is the lack of a fixed resistance; instead, the resistance is initially negligible and increases progressively with the elongation of the band. This also makes it difficult to measure changes in strength as well as monitor intensity, as they both depend on the degree of elongation. However, a modified 10-point Borg's scale has been effectively used in the past to monitor intensity for older adults exercising with EBs (Anderson et al. 2010). Moreover, EBs exert the maximum resistance at the end of the range of motion (ROM), whereas the greatest mechanical advantage of the muscles is around mid-range of ROM, which has led to the suggestion that muscles cannot be fully activated with EBs, and therefore may have a limited potential for hypertrophy and strength augmentation (Hostler et al. 2001; Aboodarda et al. 2016). Electromyography (EMG) has thus been utilized to measure muscle activation with EBs (Anderson et al. 2010; Jacobsen et al 2013). These studies have reported that there may be some exercises which produce greater muscle activation with one training method over the other, e.g. EBs result in greater activation of the infraspinatus muscle during external rotation of the shoulder, whereas free weights activate more the extensor digitorum, deltoids and trapezius during wrist extensions and shoulder lateral raise, respectively (Anderson et al. 2010). However, these findings were in young adults and secondly, may not be directly applicable to older groups since the previous exercises are mostly isolation exercises that would usually complement more complex exercises (which are of primary importance for muscle

strengthening, balance and proprioception purposes). For example, in one of the few studies that was done with young and old participants, no differences were found in leg muscle activation using EBs vs dumbbells when performing lunges with similar loads (Jacobsen et al 2013). In fact, when an overall analysis was conducted averaging all upper leg muscles, velocities and loads, the EMG activity was significantly higher with EBs ($37 \pm 1.2\%$) than dumbbells ($29 \pm 1.2\%$) ($p < 0.001$). Overall, according to a meta-analysis of trials providing EMG data from EB exercises or traditional free weights/ resistance machines (excluding isokinetic) there are no significant differences in the level of muscle activation (Aboodarda et al. 2016).

Even with exercises, such as squats, where EBs exert minimal resistance at the lowest part of the motion, the use of EBs may be advantageous for older adults. There is phenomenon called ‘the sticking point’ which limits the maximum weight that can be lifted due to the body’s lever system. For example in squats or bench presses the sticking point is at the bottom of the movement, which makes it the most disadvantaged point throughout the range of motion (ROM), thus limiting the amount of weight that can be lifted (Elliott and Wilson 1989). The sticking points also limit the force and acceleration produced (Anderson et al. 2008). Therefore, if it was possible to minimise the resistance around these points it would allow for exercise trainees to perform the movements easier and perhaps with a higher overall load and thus greater tension where the muscle is at a greater mechanical advantage (Anderson et al. 2008). For example, when trying to get up from a seated position (i.e. in a motion resembling the ‘squat’ exercise), the most challenging part is the initial push up from the chair. Therefore, with the use of elastic bands, there is no external resistance initially (apart from that of the person’s bodyweight), but it progressively increases until it reaches its maximum resistance when the person is fully up.

Moreover, EBs also challenge the muscles during the eccentric part of the movement to allow for a controlled shortening of the band and thus the muscles remain under tension, but without the fear of additional external weight. Time-under-tension is the time period during which the muscles stay engaged. It is an important factor that can lead to physiological adaptations since an increased time under tension can improve the motor unit recruitment and motor unit firing rate, and especially when the eccentric part of the movement is prolonged, it can promote hypertrophy by increasing the satellite cell number in type II muscle fibers (Toigo and Boutellier 2006; Cermak et al. 2013). Consistent with the previous example of the chair rise (or similarly with the squat exercise), it is far safer (but still challenging on the muscles) for an older person to return to the seated position in a controlled manner holding an EB than external weight (e.g. dumbbells).

With regards to changes in body composition and strength or function, although EBs have been introduced relatively recently compared to more traditional pieces of exercise equipment such as the weight-machines and free weights (e.g. dumbbells and barbells), the results have been promising. One of the first studies using EBs in older community-dwellers ($n= 62$ Caucasian women, ≥ 65 years from retirement residential communities) reported strength gains of 19.7% ($p<0.001$) in latissimus dorsi, 27% ($P<0.001$) in quadriceps and 16.5% ($p<0.01$) in pectoralis in as little as eight weeks, whereas the control group (no exercise) did not note any significant improvements), however, no information was provided regarding body composition (Damush and Damush 1999). When EBs were compared against weight-machines they were found to result in similar improvements in body composition and function of middle-aged sedentary but independent-living women, as long as the number of repetitions and intensity were similar in both protocols (Colado and Triplett 2008). In that study the rate of perceived exertion (RPE) and the number of repetitions were monitored to ensure that intensity and volume remained the same in both groups (one using the EBs and the other using weight-machines). It was noted that EBs can

be as effective as the conventional resistance equipment in increasing lean mass (+0.5 kg vs +1.0 kg, respectively, $p>0.05$ between groups), reducing fat mass (-0.5 kg vs -1.1 kg, respectively, $p>0.05$ between groups) and improving function as indicated by the significantly higher number of repetitions that participants could perform over time in knee press-ups and 60-sec squats (with no differences noted between groups). A systematic review and meta-analysis of clinical trials focusing on strength changes in adults ≥ 60 years after resistance training with EBs, noted significant improvements in strength in healthy cohorts as well as in groups with some kind of mobility limitations and even with pathologies such as type II diabetes and chronic obstructive pulmonary disease (Martins et al. 2013). The mean (\pm sd) duration of the trials, number of weekly sessions, number of sets, and average intensity were 17.6 (\pm 8.6) weeks, 2.7 (\pm 0.5) sessions week⁻¹, 2.5 (\pm 1.0) sets, and 70% (\pm 12.7) of 1RM, respectively, however a dose-response relationship could not be established between any of these factors and strength changes.

Training with elastic bands can significantly improve muscle strength and function even at home-based sessions (Zion et al 2003). Twelve adults ≥ 60 years with orthostatic hypotension performed 10 EB exercises every other day for eight weeks at home (after an initial supervised demonstration), starting from the lightest available resistance and increasing only after they could perform 10-12 reps with proper form at the end of the third and final set. Although participants did not have a fixed time schedule to complete the routine, and they could perform it in the comfort of their home, the completed sessions were ~78% and there were four dropouts (two for lack of motivation and two for other illnesses). In theory supervised classes offer better motivation and can result in greater attendance rates in older cohorts (Picorelli et al. 2014). Nevertheless, at the end of eight week home-based workout participants experienced a significant improvement in chest press, knee extension and leg press strength, with the latter being the most noteworthy change from a median 77.1 (IQR: 54.4, 149.7) kg to 197.3 (115.7, 316.2) kg ($p = 0.025$) (Zion et

al 2003). In addition, function as indicated by a timed-up-and-go (TUG) test, was improved in seven out of eight participants, with an average improvement in time of 14% ($p=0.018$). The usefulness of the TUG test is discussed further in the next section (3.2.2).

In another study where EB exercises (knee flexion/extension, squats, hip flexion/extension, ankle dorsi/plantarflexion) were compared against balance exercises (using bodyweight-only and performing exercises such as tandem walking, side steps, braiding, one-leg stance etc.) in community-dwellers ≥ 75 years exercising for eight weeks in a senior center (twice $\cdot \text{week}^{-1}$) and at home (three times $\cdot \text{week}^{-1}$), both regimens resulted in similar improvements in balance (assessed by fall index with the use of a Tetrax balance platform) and strength (assessed by dynamometry) (Cho and An 2014). Namely, strength was improved in the hip flexor and extensor, the knee extensor, the hip abductor, and ankle dorsiflexor muscles in the balance-trained group, whereas the EB trained group improved strength in all the aforementioned muscles in addition to knee flexor and ankle plantar flexor muscles. The fall index was significantly improved in both groups over time, with no significant between-group differences.

More recently, the EBs have been found effective in increasing muscle power, flexibility, balance and cardiovascular capacity in older adults after 3-6 months of 3x40min/week multi-modal exercise training programmes (Wessner 2016). The benefits of EBs have also been assessed in community-based stations where the use of EBs resulted in improved functional fitness, namely, upper limb power and lower limb muscular endurance, flexibility, lung capacity and self-perceived physical health status in older adults (Chan et al. 2016). In addition to improving body composition, strength, balance, power and function, EBs have been found effective in improving joint mobility (Sugimoto and Blanpied 2006) and quality of sleep (Chen et al. 2013) as well as reducing knee pain in older adults with osteoarthritis (Topp et al. 2002).

In terms of exercise intensity, when exercise equipment and resources are limited or high intensity exercise is prohibited due to low physical capacity to exercise, then low-to-moderate intensity exercise regimens may be implemented. Exercising at 40% of one repetition maximum (40% 1RM three times week⁻¹) produced comparable results in terms of strength with high-intensity resistance exercise (80% 1RM three times week⁻¹) in healthy older participants who were also consuming a carbohydrate (26g) and EAAs (22 g \approx 50 g intact protein) supplement within 15 minutes post-workout (Onambélé-Pearson et al. 2010). No change in body fat or body composition was noted in either of the groups. Interestingly, the low-moderate intensity group experienced a statistically significant improvement in thigh muscle thickness (from 33.6 ± 1.7 mm to 36.1 ± 1.4 mm) and the TUG test (from 5.7 ± 0.52 s to 5.1 ± 0.2 s) whereas the high-intensity group did not. Moreover, no changes in inflammatory markers was noted, which is consistent with the lack of fat loss in both groups. The differences in muscle thickness may lie in the fact that the low-intensity group performed more sessions at home (with the use of EBs) complemented by 20 mins of brisk-walking. Therefore, the two groups were perhaps not matched for exercise volume and additionally, the brisk walking sessions may have confounded the results since as discussed in Chapter 1 (*section 1.2.1*) aerobic exercise may also increase muscle size and power. Exercise volume is actually an important factor for young and older adults. In young adults, low-intensity resistance-exercise (30% 1RM) to failure has the potential to exert the same anabolic effects on muscle hypertrophy in young men as a high intensity exercise of 90% RM to failure (Burd et al. 2010). In young male participants (22.7 ± 3.1 yr), it was found that a resistance-exercise intensity as low as 16% RM followed by repeated protein feeding (~ 6 g protein every hour for 10 hrs post-workout) has been shown to keep protein synthesis rates significantly higher than resting levels (Bechshoeft et al. 2013). When older adults (70 ± 5 yr) perform exercises at similar intensities with young adults but at higher total volumes then they can experience comparable rates of muscle

hypertrophy (Kumar et al. 2012). For example the mean area under the curve (\pm SD) of muscle protein synthesis within four hours of performing three sets vs six sets of resistance exercise at 40% 1RM in young was 0.07 (\pm 0.02)% vs 0.06 (\pm 0.02) % ($p>0.05$) but in old 0.01 (\pm 0.01) % vs 0.13 (\pm 0.03)% ($p<0.01$), respectively (Kumar et al. 2012).

The previous finding indicates that increased exercise volume and a frequency of three sessions per week, may potentially reduce the ‘anabolic resistance’ phenomenon. Perhaps this is the reason why no muscle mass increase was noted in the study by Balachandran et al. (2014) with sarcopenic obese older adults (discussed in detail in *Chapter 2*). That is, exercising twice a week with three sets of 10-12 reps per exercise may not be enough to elicit a hypertrophy response in older adults, and especially when protein intake is not taken into consideration. Nevertheless, exercising at moderate intensities (\sim 50% 1RM) and trying to perform the concentric part of the exercises explosively and the eccentric part slowly, can be effective in improving power in sarcopenic obese older adults (Balachandran et al. 2014). An interesting protocol with protein supplementation from different sources (2 x 20 g whey or collagen daily for a year) differing volume and intensity workouts, that can provide valuable data for all these different factors has been developed by Bechshoeft et al. (2016), but the trial findings are yet to be published. All the previous studies discussed in this section are particularly important and have informed the current protocol which cannot accommodate the use of free weights/machines or high intensities due to low practicality and/or discouragement of participants. Therefore, exercising at low-to-moderate intensities but at a higher overall volume may be a beneficial strategy for body composition and functional changes in older adults.

In terms of frequency and duration, although a few exercise routines have shown the potential to increase strength when performed only once or twice a week (Di Francisco-Donoghue et al. 2007;

Sousa et al. 2013), such studies refer to protocols using increased volumes (e.g. repetitions to volitional fatigue) and/or have been conducted in healthy older adults and not sarcopenic obese. It is usually recommended that an exercise protocol is performed at least 3 times·week⁻¹ in order to elicit significant improvements in various fitness components and not just absolute strength (ACSM 2014). The ACSM also recommends that a mixed exercise programme should be performed 3-5 times·week⁻¹ to allow for various physiological adaptations. For example, a combination of resistance, aerobic and balance exercises that takes place 3 times·week⁻¹ at moderate intensities, has the potential to improve co-ordination, balance and prevent falls (Baker et al. 2007). Exercising for > 150 mins week⁻¹, even at low-moderate intensities, can promote physical independence and longevity, and increase disability-free life expectancy (McPhee et al. 2016). This is in accordance with a meta-analysis by Steib et al. (2010) and the ACSM reports (ACSM 2009; Garber et al. 2011) suggesting that neuromotor exercise training that involves power, agility, balance and proprioceptive training needs to be performed 2-3 times·week⁻¹ even at moderate intensities in order to improve muscle power and reduce the incident of falls in older adults. The duration of mixed exercise interventions and those incorporating EBs is usually 30 – 60 min with a varied proportion of time allocated to different fitness aspects (Baker et al. 2007; Martins et al. 2013). In group classes it is usually established that the first 10-15 min are used for warming up exercises, the main body of the class lasting from 30-50 min is dedicated to strength, aerobic and balance exercises, whereas the final part should be used for activities of low impact and effort such as flexibility exercises in order to let the participants cool down appropriately (ACSM 2014). Such protocols have been found to have moderate to high attendances from ~62% for community-based classes, up to 100% for research centre-based classes when full attendance is required for the research purposes (Baker et al. 2007).

Regarding practicality and delivery of the exercise programme, the use of chairs and EBs allows participants to perform the same exercises all together and thus, gain a better appreciation of the exercise techniques by looking at each other as well as immediate feedback from the instructor. After an initial training period during which participants can familiarise themselves with the different requirements of the training protocol using only chair-based body-weight exercises, the introduction of elastic bands can help them maintain and gradually improve their balance, dynamic movement and kinesthetic awareness (Baechle and Westcott 2010). An extra advantage of the elastic bands is that participants can adjust the resistance quickly and relatively effortlessly either by holding the band at a different length or by selecting a band of different thickness. If participants were instructed to use free-weights or resistance machines they would have to let the weights down and pick up new ones or get in and out of the machine in order to change the intensity. That scenario would have a very low practicality during a group session with older adults.

It is important to note that although exercise training may elicit significant improvements in physical function, performance and potentially body composition, it has been hypothesized that the benefits in older populations may rely more on losses of fat mass than changes in lean mass (Santanasto et al. 2010). After comparing exercise training alone with exercise and diet-induced weight loss they reported that improvements in physical function, as indicated by a mean SPPB score change (\pm SD) of $+0.7 \pm 1.4$, were significantly associated with abdominal and intermuscular adipose tissue losses but not with changes in lean mass or strength in overweight older community-dwellers. In fact, appendicular lean mass and strength were significantly lower after six months of exercise plus diet by 0.9 ± 0.8 kg and 16.8 ± 17.9 N · m, respectively. Nevertheless, SPPB score was significantly improved. Interestingly, the exercise-only group did not notice any significant changes in muscle mass, fat mass, strength, or function, which could suggest that the exercise programme was not challenging enough to elicit any physiological adaptations. Thus, all

improvements in the exercise and diet group could be attributed to fat loss. This could be accounted for by the fact that the exercise routine was relying heavily on walking and less on resistance and balance exercises (40-min, 10-min, and 10-min respectively), whereas frequency (3 sessions·week⁻¹ for the eight first weeks and twice week⁻¹, for the following 16 weeks) and volume (2 sets x 10 reps) might have been less than optimal. Therefore, it could be proposed that when muscle mass and/or strength cannot be improved then fat loss alone may be beneficial for activities that require a movement of bodyweight around space.

Although resistance exercise alone (3 sets x 10 reps at 70% 1RM three times week⁻¹) has been effective in reducing intermuscular fat and enhancing function in sedentary overweight/obese older adults, those with the highest levels of adiposity at baseline, experienced the smallest improvements after a 5-month intervention (Nicklas et al. 2015). Therefore, baseline adiposity plays a role and can be a confounder in such interventions. Moreover, it was noted that moderate-intensity exercise in combination with caloric restriction (600 kcal) resulted in greater improvements in some indices of performance (self-reported disability and 400-m walk time) compared to exercise alone, but overall there were similar improvements in both groups (e.g. for knee-extension strength, power, 4-m gait speed). In an 18-month trial, a moderate-intensity physical activity programme for 288 older overweight and obese men and women, resulted in significant improvements in body composition only when physical activity was combined with a weight-loss programme (daily energy deficit 300-500 kcal) that promoted significant losses of fat mass; on average 4.9 kg fat mass was lost (Beavers et al. 2014). In the same study, although a significant amount of lean mass was lost (~2.5kg) that was outweighed by the substantial loss of fat mass which resulted in an improved ratio of fat to lean mass as well as in improvements in mobility and cardio-metabolic risk factors at the end of the study. Similarly, Wang et al. (2007)

reported greater improvements in muscle strength and quality with greater losses of fat mass, even at the expense of lean mass, after an exercise and hypocaloric diet programme.

In conclusion, the addition of an exercise training programme to the lifestyle routine of older people is very important. Resistance exercise with the use of elastic bands can be an effective strategy when free weights or exercise machines are not available or realistic. Exercise training can improve older adults' functional abilities whilst it has the potential to increase their lean mass, as long as it is performed three times weekly at low-moderate intensities and adequate volume. It seems however, that in overweight and obese older adults, the loss of adipose tissue is equally vital not only for cardio-protective reasons but for improved physical functioning as well. Therefore, the addition of a nutritional regimen may work in synergy with an exercise routine for the optimization of physiological changes in older sarcopenic and obese adults.

3.1.2 Nutritional regimen and supplementation

There are many parameters that need to be considered before designing a nutritional intervention for older adults, especially when a food product and/or a supplement are introduced to the diet. The most important factors include the quality, quantity and volume of food, type, frequency, timing and more practical issues such as palatability, sustainability over a long period of time as well as handling, delivery and storage of the foods/supplements. In this study, the main nutrient of interest is protein therefore, all the aforementioned parameters were carefully considered when designing the most appropriate ‘food vehicle’ that can deliver extra protein without compromising the diet’s overall quality, practicality and easiness of use. The rationale for the addition of supplementary vitamin D will also be discussed.

To tackle the development and progression of sarcopenic obesity two seemingly contradicting conditions need to be met simultaneously; that is, gaining or preserving muscle mass and strength, while losing fat mass (Goisser et al. 2015). Weight loss diets via energy restriction (from <500 to 800 kcal deficit) have been found effective in reducing body weight, however the weight loss is accounted for not only by reduced fat stores but also substantial losses of lean mass, as shown in a meta-analysis of weight-loss trials in middle-aged and older adults (Weinheimer et al. 2010). Even modest reductions of energy intake ~250 kcal can produce such lean mass losses (Weinheimer et al. 2010) and therefore, weight loss regimens via reduced energy intake in older sarcopenic obese adults remain a topic of controversy (Waters et al. 2013; Goisser et al. 2015). Although the addition of exercise to a hypocaloric diet can synergistically enhance the utilization of fat (Amati et al. 2008) and minimise the losses of lean mass, it is still likely that some lean mass (mainly muscle tissue) will be lost (Weinheimer et al. 2010). This is not surprising considering that exercise alone can stimulate muscle protein synthesis but without the availability of substrates

for tissue synthesis, the net protein balance may remain negative. Therefore, an adequate protein intake alongside a resistance exercise protocol has the potential to attenuate the reduction in muscle protein synthesis rates during periods of energy restriction in young and older adults (Areta et al. 2014; Murphy et al. 2015). It is generally agreed that when an energy-deficit plan along with regular exercise training is undertaken, then an increased protein intake in the range of 1.2-1.5 g · kg bw⁻¹ or ~30% of total daily energy intake is mandatory to mitigate reductions in MPS (Leidy et al. 2007; Wolfe et al. 2008; Morley et al. 2010; Deutz et al. 2014; Paddon-Jones and Leidy 2014). Protein intakes providing such ranges have been found more effective in promoting fat loss and preserving lean mass during caloric restriction compared to low-to-moderate protein diets, e.g. 0.5-0.9 g · kg bw⁻¹ (≈16-21% energy intake) (Wycherley et al. 2012; Goisser et al. 2015). Protein intakes around the 1.3 g · kg bw⁻¹ range have the potential to attenuate the fall in MPS rates during hypocaloric diets (-750 kcal) in young, middle aged and older overweight/obese adults (52± 2 yr, 34.7± 1.1 kg m⁻²) (Hector et al. 2014). In addition to an increased anabolic response, high intakes of dietary protein can elicit favourable effects upon adherence to an energy-restricted diet, via increased satiety and perception of the eating-related feeling of pleasure, which can be an important factor especially in obese adults (Leidy et al. 2007).

Increased intakes of protein and dairy protein in particular (30% and 15% of total energy intake, respectively), may be able to attenuate, or even reverse, the loss of muscle mass in middle aged adults especially during periods of reduced energy intake (Josse et al. 2011). Although the maximum anabolic response to protein feeding in a single meal has not been fully elucidated in older adults, it has been proposed that 40 g of whey protein, or potentially even more if a whole body training session has preceded the protein feeding, should be consumed to optimally stimulate muscle protein synthesis in older adults (Hamilton et al. 2016). It has also been suggested that although both whey and casein are milk proteins, whey has a more pronounced effect on the acute

stimulation of muscle protein synthesis in older adults compared to casein (Dangin et al. 2003; Burd et al. 2012). The enhanced anabolic properties of whey protein have been attributed to its higher leucine content when compared to casein and milk solids; 1g of whey, casein and milk solids contain 108 mg, 82 mg and 77 mg leucine, respectively (Philips et al. 2009). Since whey protein has approximately a 30% higher leucine content compared to casein -which is the most abundant protein in milk-, the equivalent of 40g whey in terms of leucine content would be ~52 g of casein or 56 g skimmed milk powder (\approx 3 pints of semi-skimmed milk).

As discussed in Chapter 1, the timing of protein administration may not be crucial for hypertrophy (as long as the total daily protein intake is sufficient $\sim 1.2\text{-}1.5 \text{ g} \cdot \text{kg bw}^{-1}$), however, there may be timings of protein feeding that could potentially offer benefits to older adults. Overnight sleep is perhaps the longest post-absorptive period during which net protein balance remains neutral (i.e. muscle protein breakdown \simeq muscle protein synthesis) (Groen et al. 2012). Thus, it may provide a ‘window of opportunity’ for a protein feeding to elicit higher aminoacidemia and maintain elevated MPS rates. Trials measuring the acute response to protein have shown that 40 g casein can increase MPS and maintain a positive net protein balance during the night hours, with/out the addition of an evening exercise session in young and older adults (Groen et al. 2012; Res et al. 2012). Therefore, pre-sleep protein feeding may offer a pragmatic approach to increase total protein intake, and elevate MPS rates during the night, which may have an additive effect on total daily muscle protein synthesis and attenuate muscle loss, however, no studies have employed this protocol in sarcopenic obese older adults. Moreover, casein offers a more sustained and prolonged appearance of amino acids in blood compared to whey, whereas the latter produces a higher but more transient effect of aminoacidemia and thus MPS over periods of \sim six hours (Pennings et al. 2011b). Therefore it could be hypothesised that milk protein that contains fractions of both proteins would be the best approach for pre-sleep feeding in sarcopenic obese older adults.

Although requiring further corroboration, dairy products may be also beneficial for fat loss purposes (Zemel 2004a; Josse et al. 2011). Previous research has suggested that the fat-loss properties of dairy products in obese populations may be accounted for by their high calcium content, which may promote increased lipid utilization especially from the trunk combined with an energy restriction diet (1100-1300 mg Ca^{2+} day⁻¹, and 500 kcal daily deficit, respectively) (Zemel 2004b; Zemel et al. 2005). In those studies a hypocaloric diet with the addition of extra calcium coming from supplements or dairy products while the rest of the macronutrients were similar in the control (~500 mg Ca^{2+} day⁻¹) vs intervention groups (1100-1300 mg Ca^{2+} day⁻¹), resulted in greater fat losses for the high dairy groups with an extra of ~2kg of fat lost compared to control, and ~50% more fat lost from the waist region. Calcium intake has also been inversely associated with the metabolic syndrome and sarcopenia in middle-aged and older adults, even after adjusting for several factors, such as age, physical activity, smoking and energy intake (Liu et al. 2005; Seo et al. 2013; Lee et al. 2014)

Another important micronutrient is Vitamin D. As reported in Chapter 1, Vitamin D deficiency in older individuals is associated with muscle atrophy, low muscle strength, increased risk of falls and bone fractures and increased risk of mobility limitations and disability (Snijder et al. 2006; Ceglia 2008; Houston et al. 2013). The UK Department of Health (2012) and SACN (2016) advise that people aged 65 years and over should take a daily Vitamin D supplement of 10 µg (equal to 400 International Units (IU)) since the dietary intakes are not sufficient as discussed in Chapter 1 section 1.2.3.4. A systematic review assessing the effectiveness of vitamin D supplementation without the addition of exercise in people over 60 years, concluded that daily oral administration of 800-1000 IU (20-30 mcg) of Vitamin D had beneficial effects on strength and balance (Muir and Montero-Ontasso 2011). Furthermore, it has been suggested that for sarcopenic obese older

adults, doses higher than 1,000 IU vitamin D day⁻¹ may be required since sarcopenia, obesity and sarcopenic obesity are associated with vitamin D deficiency (Villareal et al. 2011a; Kim et al. 2013a). Therefore, vitamin D status may be a confounding variable for any intervention aiming at improvements in strength, muscle mass and functional ability in older sarcopenic obese adults.

In 2010, an expert panel convened by the Society for Sarcopenia, Cachexia and Wasting Disease developed a report with nutritional recommendations for the management of sarcopenia (Morley et al. 2010). The panel's guidelines state that adequate protein can slow the progression of muscle atrophy, however, the optimal strategy against sarcopenia includes exercise (resistance and aerobic) along with a high-protein intake (up to 1.5 g · kg bw⁻¹) which would be ideally complemented by adequate vitamin D intakes. Therefore, in order to avoid vitamin D deficiency and any confounders that may arise from very low serum 25(OH)D concentrations, it would be prudent for studies (especially in countries with a low exposure to sunshine and for vulnerable groups such as those aged ≥ 65 years) to supplement their diets with at least the minimum recommended amount of Vitamin D (10 µg daily ≈ 70 µg weekly) (UK Chief Medical Officers 2012; SACN 2016).

An ongoing study proposes that a high-protein supplement containing beta-hydroxy-methyl-butyrate (HMB; a leucine metabolite) and vitamin D may be beneficial for sarcopenic older patients with a hip fracture (Malafarina et al. 2013). Since ~40% of the older adults do not manage to recover their functional capacity after a hip fracture (Uriz-Otano et al. 2015) it was hypothesized that an oral supplement containing ~ 18.3g milk protein, 500 IU (12.5 µg) vitamin D3 and 1.2g HMB administered twice a day would have a significant effect on functional recovery and muscle mass of older patients (Malafarina et al. 2013). According to preliminary findings, the oral supplement attenuated the loss of muscle mass and weight (which significantly declined in the

control group), but there was no impact on fat mass, strength, gait speed, physical function and inflammatory markers (Malafarina et al. 2017).

Although nutritional interventions characterised by a high protein intake have shown great potential, the actual intake of high protein foods seems to decline with age (Nieuwenhuizen et al. 2010; Tieland et al. 2012b). There are certain barriers that can account for this decline, such as deterioration in appetite, impaired vision, dementia, deterioration in dentition and physical skills, medication, changes in gut function, and reduction in chemosensory abilities (Best and Appleton 2013). For example, the number and efficiency of taste buds may deteriorate with age, resulting in impaired perception of taste especially in sweet and salty foods, which may start to taste more sour or bitter (Omran and Morley 2000).

Therefore, palatability, taste and effort required to prepare the meals are often some of the most important parameters that can facilitate the consumption of high-protein meals in older adults (Best and Appleton 2013). Thus, the most realistic way of increasing an older individual's protein intakes in a sustainable and practical way without probing them to purchase more and/or non-habitual foods would be through an oral supplement. Oral nutritional supplements have been found to be effective in delivering an increased amount of protein to institutionalized and community-dwelling older adults; always bearing in mind that a variety in sensory attributes is essential in order to avoid the phenomenon of 'taste fatigue' (i.e. daily consumption of the same exact meal) and thus, promote compliance (Nieuwenhuizen et al. 2010). Therefore, the use of a ready-to-drink milk-based liquid supplement that comes in a variety of flavours offers advantages that can overcome all the aforementioned issues. From a nutritional perspective, the supplement must have the desired amount of protein (>40 g) along with a favourable amino acid profile, especially in relation to leucine. Therefore, the current protocol includes the use of an affordable commercially

available liquid dairy supplement with a protein and leucine content of 50 g and 6 g, respectively. These quantities are sufficient to trigger a significant response in muscle protein synthesis rates as outlined in this chapter and discussed in more detail in Chapter 1. Moreover, the selected drink has a long shelf-life of approximately eight months, a period during which it can be stored at room temperature. If opened but not consumed immediately it can be stored in the fridge for three days. The four different flavours (vanilla, chocolate, strawberry and banana) ensure that most preferences are likely to be accommodated. It is also proposed the use of an affordable and commercially available vitamin D supplement containing 25 µg vitamin D3 per tablet. The nutritional plan will be supplemented by a simple exercise training routine, using chairs, elastic bands and the bodyweight of the trainees as exercise aids with resistance, aerobic, stretching and balance elements.

In conclusion, a moderate energy-restriction diet with a high protein intake in the range of 1.2 - 1.5 g · kg⁻¹ day⁻¹ accompanied by exercise training three times weekly for 24 weeks may have the potential to improve older adults body composition and physical function (**Table 3.1**). Apart from the total protein intake it is important to administer one meal during the day with a protein content high enough to optimally stimulate muscle protein synthesis either after the exercise training or before sleep. Pre-sleep ingestion of protein may offer additional benefit by utilizing the overnight hours during which net protein balance usually does not benefit muscle tissue accrual. The lifestyle intervention can be supplemented with vitamin D to avoid confounders related to low serum 25(OH)D and ensure adequate calcium absorption. An outline of the strengths and rationale of the present protocol is presented in **Appendix 3**.

Table 3.1 Proposed protocol for a dietary and exercise interventions in Scottish older adults with sarcopenic obesity.

Dietary protocol		Exercise protocol (common for both groups)
Intervention (exercise + diet: EXD)	<ul style="list-style-type: none"> • 500 kcal caloric deficit • ~1.5 g protein · kg bw⁻¹ • Protein supplementation (50g milk protein day⁻¹) post-workout or before bed on the non-exercise days. • ~70 µg Vitamin D3 week⁻¹ 	<ul style="list-style-type: none"> • Three hourly sessions weekly • Resistance, balance, aerobic and flexibility exercises of low-to-moderate intensity. • Progressive increase in resistance, complexity and speed of contraction, starting with seated bodyweight and moving onto increased resistance using elastic bands.
Control (exercise only: EX)	<ul style="list-style-type: none"> • Habitual diet • ~70 µg Vitamin D3 week⁻¹ 	

3.2 Assessment methods

Designing lifestyle interventions requires the existence of methods/tools able to detect and measure changes in the desired outcomes with sufficient validity and reliability. In the context of ageing muscle, the advancements in technology have provided scientists with diverse tools and techniques to measure the size/ mass of the different body compartments, and in particular skeletal muscle and fat mass. Furthermore, the body's functionality and capacity to perform physical tasks is a crucial aspect affecting the life quality of individuals. Especially in older age where a certain degree of decline in physical performance is expected, maintaining high levels of strength and functionality is paramount. Therefore, in this section an analysis of the reliability, validity and practical differences of the main methodological approaches to measure changes in body composition, muscular strength and physical function is provided.

3.2.1 Body composition

In the past years many initiatives have taken place in order to reach a consensus for the definition of sarcopenia and sarcopenic obesity (Baumgartner and Waters 2006; Cruz-Jentoft et al. 2010; Donini et al. 2013). Depending on the definition criteria, the methodological approach and the tools to assess body composition can change. These tools can offer different methodological robustness (reliability and validity) and practical applications. This section will discuss the properties of key scientific tools and methodologies to measure body composition changes, particularly in muscle and fat mass. Moreover, the feasibility and practicalities of such tools will be evaluated especially in the context of measuring body composition changes in community-dwelling older adults.

Although, the use of body mass index (BMI) is used widely to classify obesity, it is not sensitive in identifying high adiposity (Okorodudu et al. 2010). Particularly a BMI $\geq 30 \text{ kg}\cdot\text{m}^{-2}$ is likely to mask sarcopenia in older people (Newman et al. 2003a). A meta-analysis by Okorodudu et al. (2010) concluded that BMI failed to detect half of the cases of adults with a high percentage body fat (%BF). Not only does body mass index underestimate body fatness, it also fails to provide any information about the distribution of fat (Villareal et al. 2005). For any given BMI, women are more likely to express higher adiposity than men (Gallagher et al. 1996) and Asians than Caucasians (Chung et al. 2013). Similarly, individuals with low muscle mass will have by definition a higher percent body fat compared with their healthy counterparts for a given BMI. Therefore, since the current study focuses on older adults with low muscle mass, the use of BMI as the only obesity criterion would not be suitable. An appreciation of the importance of the different physiological characteristics of people with similar BMI but different levels of adiposity is presented in **figure 3.1**.

Two of the ‘gold-standard’ methods to measure body fat and muscle mass are magnetic resonance imaging (MRI) and computed tomography (CT) since they have the advantage of calculating segmental and total muscle mass, as well as discriminate between visceral and subcutaneous adipose tissue (Van der Kooy and Seidell 1993; Sampaio et al. 2006; Malafarina et al. 2012). They can also assess the degree of fat infiltration in the muscle tissue, which is a valuable indicator of muscle quality, especially in the ageing muscle (Marcus et al. 2013). Although MRI and CT are considered valid and reliable for the assessment of body composition they are not used routinely to detect sarcopenic obesity firstly due to the high cost and secondly because they require specialised software and highly-trained staff. Moreover, they are time-consuming and not easily accessible as patients are required to travel to the test centre. Therefore, it is not of high practical

value for field studies. In addition to these, another key limitation of CT is the considerable amount of exposure to radiation for the patients (Sampaio et al. 2006).

Dual-energy x-ray absorptiometry (DXA) has been routinely used for the assessment of bone mineral density and the detection of osteoporosis. In the past years its applications have been expanded to a 3-compartment (bone, fat and lean mass) model of body composition assessment. It takes only 3 minutes for a whole-body scan and the amount of exposure to radiation is only minimal. One of its biggest limitations, that can especially affect obesity interventions, is that the thickness of the scanned body part may affect the measurements (Schoeller et al. 2005). This can result in systematic differences between obese and lean individuals, or in errors between serial measurements in people trying to gain or lose weight. Moreover, the presence of bones and/or calcification of soft tissues, e.g. in the aortas of older adults, can negatively affect the results of a regional soft tissue analysis (Lee and Nieman 2007). Although it is cheaper than CT and MRI it is neither sufficiently affordable nor easily accessible to the general public to be used as a routine tool for the detection of sarcopenic obesity. Therefore, it is mainly used for research purposes in clinical settings or university labs.

Bioelectrical impedance analysis (BIA) is a popular, non-invasive and quick technique in measuring body composition. A BIA device creates an electrical current that passes through the body. The device can measure the resistance (created by the non-conducting tissues and mainly fat) of the body to the current. The resistance value is used to calculate body-fat and fat-free mass. BIA is a reliable instrument to measure total body water (Lee and Nieman 2007), however, its ability to estimate fat-mass, fat-free mass and skeletal muscle mass depends heavily on the regression equation used (Haapala et al. 2002). Another weakness of BIA is the assumption that participants are normally hydrated, however this may not be the case in individuals who, prior to

the assessment, have consumed alcohol, have exercised or taken drugs that can affect the water and electrolyte balance of the body (such as diuretics). However, if a standardized protocol is used along with a regression equation developed for a specific population group, BIA can be a convenient and reliable instrument with high concurrent validity for the assessment of body composition in young and older adults (Janssen et al. 2000; Lee and Nieman 2007; Mijnders et al. 2013). One of the most reliable equations for the estimation of skeletal muscle mass by BIA was produced by Janssen et al. (2000) who cross-validated the BIA results of 388 men and women aged 18-86 years of age against their MRI-derived results and reported an r^2 of 0.86 and a SE of the estimate (SEE) of 2.7 kg in Caucasians, Hispanics and African-Americans.

Other body-composition assessment techniques that could be performed at a patient's home or at non-clinical environments include calf and mid-upper arm circumference as well as skinfold thickness. Although these tools are portable, non-invasive and practical, they have shown a low association with DXA and are not highly recommended for older individuals if other more reliable equipment is available (Haapala et al. 2002; Rolland et al. 2003). However, anthropometrical tools can provide scientists with useful information, such as an estimation of fat distribution. It is well documented that abdominal fat (subcutaneous, visceral and intrahepatic) which is a risk factor for metabolic diseases and insulin resistance, increases with age (Beaufre et al. 2000). When a cross-sectional analysis technique for the measurement of abdominal fat is not available for field studies then simple anthropometric methods can be used, such as the sagittal abdominal diameter (SAD). The sagittal abdominal diameter test involves a simple anthropometric measurement (in a seated or supine position) that has been associated with cardiometabolic risk factors (Pouliot et al. 1994; Iribarren et al. 2006; Sampaio et al. 2007; Anunciacao et al. 2014). It has a high validity in identifying abnormally high abdominal fat that may pose a health risk when compared against CT ($r=0.80$, $p<0.001$ in women and $r=0.64$, $p<0.001$ in men) and MRI (standing SAD vs MRI: $r=0.94$,

$p < 0.001$, supine SAD vs MRI: $r = 0.93$, $p < 0.001$), and high reliability (intra-class coefficient of 0.99) (Van der Kooy et al. 1993; Sampaio et al. 2007). Standing SAD is positively associated with age, blood cholesterol, hypertension and type II diabetes, and inversely associated with education (Iribarren et al. 2006). When adjusted for age and race, a SAD of ~26 cm can increase the hazard ratio HR (95%CI) of coronary heart disease by 1.70 (1.57, 1.83) in men, and 1.79 (1.63 - 1.96) in women (Iribarren et al. 2006). This is in agreement with Pouliot et al. (1994) who has proposed cut-offs of SAD > 25cm being indicative of an increased risk for atheromatic metabolic disorders, and related to increased fasting and insulin concentrations. A cut-off of ~25 cm for standing SAD may also indicate an increased age-adjusted risk of sudden death [(RR(95%CI): 4.1 (2.0-8.3), $p < 0.001$], as noted in a study with middle aged French men (43 – 52 yr; $n > 7,000$) who were followed up for 23 years (age at follow-up assessment 66-75 yr) (Empana et al. 2004). The relative risk for sudden death remained significant [2.6 (1.0 to 6.7)] even after further adjustments for smoking, blood pressure, trunk subcutaneous fat, type II diabetes and plasma cholesterol concentrations. Other studies have suggested that even lower cut-offs of ~ 20 cm may predict increased risk of CVD (Sampaio et al. 2007; Riserus et al. 2010), however these studies measured SAD in a supine position which is known to depress abdominal fat due to gravity, which may explain the lower cut-offs (Sampaio et al. 2007). Finally, SAD has been used to assess changes in abdominal adiposity in older women undergoing a weight-loss programme (Mazzali et al. 2006)

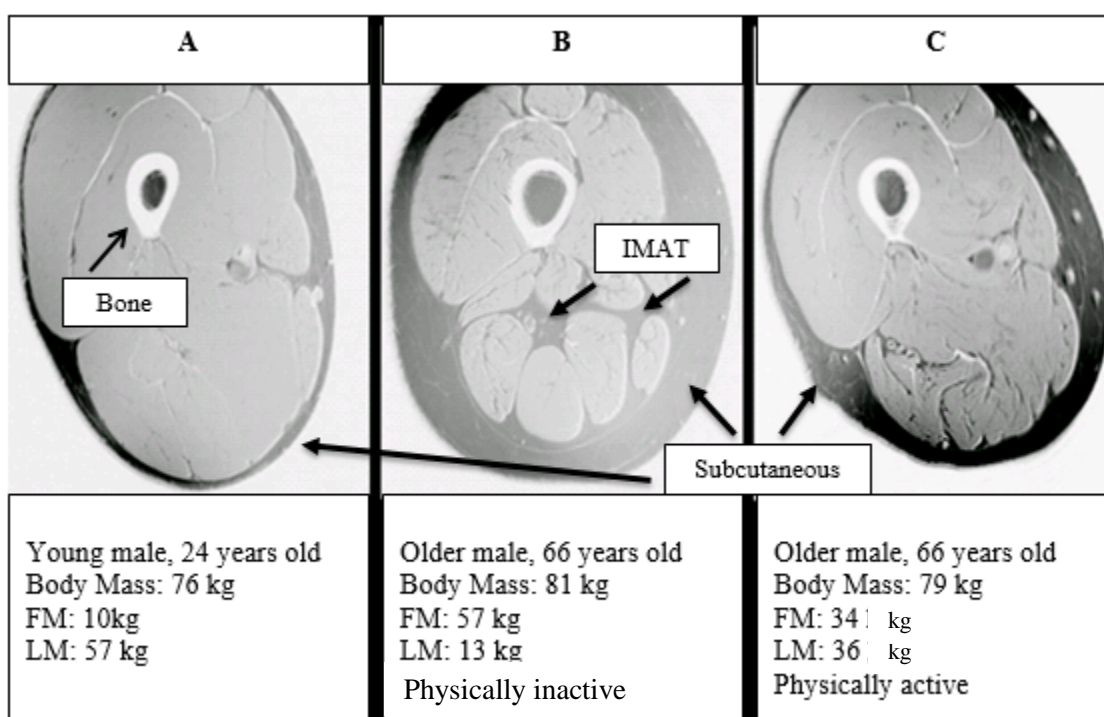


Figure 3.1 Differences in skeletal muscle mass (light grey) and adipose tissue (subcutaneous and intermuscular; black outer tissue) between three men of similar bodyweights. MRI images depict skeletal muscle architecture in young (A), old-inactive (B) and old-active (C) males. The white tissue in the middle represents the bone. IMAT, intermuscular adipose tissue; LM, lean mass; FM, fat mass.

[Adapted by McLeod et al. (2016) and used under the terms of the Creative Commons Attribution 4.0 International License found at <http://creativecommons.org/licenses/by/4.0>, changes have been made to the text, and colours of the cross-sectional images).

3.2.2 Strength/function

The loss of muscle function has been included in the consensus for the definition of sarcopenia by the International Working Group on Sarcopenia (IWGS) and the loss of muscle strength and/ or physical performance in that of the European Working Group on Sarcopenia in Older People (EWGSOP). Therefore, assessing strength and function/performance is very important in older age. There are various methods available to measure strength, including but not limited to: chest press, leg press, pull down, handheld dynamometry, isokinetic dynamometry, knee flexion/extension and vigorometer, whereas some of the most popular tests for function are gait

speed, functional reach, the Fullerton functional fitness test, the Short Physical Performance Battery test (SPPB), sit-to-stand, stair climb and the timed up and go test (Cruz-Jentoft et al. 2010; Mijnaard et al. 2013).

The timed 'Up and Go' (TUG) test is a quick tool for the assessment of functional mobility in older adults (Podsiadlo and Richardson 1991). It does not require any special equipment or training to perform and is reliable with good intra-rater and inter-rater variability. It is highly associated with the Barthel Index of ADL ($r=0.78$) and can predict the ability of an older individual to go outside safely (Podsiadlo and Richardson 1991). The use of TUG test has been recommended by the American and British Geriatric societies as a screening tool for falls (Panel on Prevention of Falls in Older Persons 2011) and by the National Institute of Clinical Evidence (NICE) for the assessment of balance in the falls prevention guidelines for older adults (NICE 2013). Interestingly, TUG is not just a simple functional mobility test but it is also associated with slow cognitive processing speed and executive function (Donoghue et al. 2012), as well as cognitive impairments and poor motor control due to asymptomatic brain atrophy or cerebrovascular damage (Kose et al. 2016).

The SPPB test includes three simple tests, 1) gait speed, 2) static balance and 3) five repeated chair stands (RCS), the results of which can reliably predict institutionalisation and mortality rates (Guralnik et al. 1994; Cooper et al. 2010). Older individuals with low SPPB scores (≤ 10) at baseline had a higher risk of mobility limitations, and in particular loss of the ability to walk a distance of 400m after a 3-year follow up (Vasunilashorn et al. 2009). Moreover, poor performance in SPPB has been associated with abnormal pulmonary function and therefore, SPPB can be potentially used as an early screening tool for the prediction of impairments in pulmonary function in older age (Choi et al. 2012). The gait speed test in SPPB has been previously suggested

to independently predict risk of falls, decline in function and health, hospitalization and mortality, both in well-functioning older adults and in older clinical populations (Cesari et al. 2005b; Studenski et al. 2003). Similarly, the RCS test is a quick and reliable test for the assessment of lower limb strength with excellent intra-rater, inter-rater and test-retest reliability in healthy older community-dwellers and stroke survivors (Bohannon 2007; Mong et al. 2010). It can also predict the risk of recurrent falls in community-dwellers ≥ 65 years (Buatois et al. 2008). When the RCS test was compared against other tests such as the 6-meter walk, the half-turn or the pick-up-weight test, it was found to be the best in terms of predictive validity and feasibility (Tiedemann et al. 2008).

Although lower extremity strength may be more important for functional abilities than upper body strength (Samuel and Rowe 2012), grip strength is one of the few tests that has consistently shown high intra-rater and inter-rater reliability as well as high construct and concurrent validity (Mijnared et al. 2013). Additionally, low hand grip strength has been associated with increased risk of falls (Sayer et al. 2006), disability (Rantanen et al. 1999), increased length of hospitalization (Kerr et al. 2006), low health-related quality of life (Syddall et al. 2005) and increased risk of mortality (Laukkanen et al. 1995). Apart from reliability, the main advantage of handgrip dynamometry compared to other strength tests is that it is portable and can be performed quickly at any setting (clinical or non-clinical) without the need for large equipment or specialized computer software.

One other important aspect of function is balance (static and dynamic). Whereas the tandem balance test in SPPB provides an indication of static balance capacity, the 1-arm functional reach is a screening tool for dynamic balance, which is equally important in older adults (Cech and Martin 2012). The functional reach test can detect impairments in balance or changes in balance

performance and is a reliable, precise, quick and portable screening tool for the margin of stability in older adults (Duncan et al. 1990).

In summary, although the assessment of concurrent validity is disadvantaged by the lack of gold standards when assessing muscle strength and performance, it has been suggested that handgrip strength and SPPB are two valid and reliable tools for the assessment of strength and physical performance in older community-dwellers. Finally both TUG and the functional reach test are quick and reliable functional-balance and mobility tests that have been used consistently as screening tools for the prediction of falls and mobility performance in older populations.

3.2.3 Quality of life

One of the main aims of researchers is to promote physiological adaptations that can be eventually translated into a better sense of well-being. Therefore, the goal of many intervention studies is to help people improve their health-related quality of life (HRQoL). For example, the benefit of increasing the size of the knee extensor and flexor muscles for an older individual is of minor practical significance if it is not accompanied by an increment in some or all of the fitness components such as strength, power, agility, muscular endurance, cardiovascular endurance, which may eventually translate into better balance, co-ordination, physical function and ability to perform everyday activities. These aspects will affect the individual's perception of his/her life quality.

One of the most valid and reliable tools to measure HRQoL is RAND 36/ SF-36. It has been translated, modified and adopted by researchers and clinicians in 45 countries (Hays and Morales 2001). The test has good construct validity and internal consistency (Lyons et al. 1994). It takes

only 7-10 minutes to complete, and has been used in studies assessing quality of life in older individuals with a wide range of conditions, from independent-living community-dwellers to hospitalised patients (Hays and Morales 2001). It takes into account eight health-related concepts: physical functioning, limitations related to physical health issues or emotional problems, social functioning, energy and fatigue, emotional well-being, health perceptions, pain and a single item on changes in perceived health over the last year.

3.3 Summary

In summary, findings from published studies favour the use of a dairy product with a high-protein content alongside a moderately hypocaloric energy intake in order to promote fat loss while accruing skeletal muscle tissue. Vitamin D is a micronutrient of vital importance for calcium absorption, bone health and potentially physical function of older adults, especially in countries with low levels of exposure to sunshine. Exercise training has been consistently found to be beneficial for many aspects of physical function and should be included in every lifestyle. Therefore, the current protocol proposed the use of a commercially available liquid dairy supplement with a high content of milk protein (~50 g) to ensure at least one meal per day has adequate protein to achieve ‘optimal’ muscle protein synthesis. That meal could be consumed after the exercise session, or before bed on the non-exercise days. The high-protein milk could also aid in increasing the total daily intake of protein to $1.2 - 1.5 \text{ g protein} \cdot \text{kg bodyweight}^{-1}$ during a hypocaloric diet (~500 kcal deficit). A realistic exercise programme employing affordable equipment (elastic bands) and exercises (bodyweight, resistance, flexibility and balance) that can be easily replicated in a community setting, was also employed. The assessment protocol has been designed for field studies, without however, compromising validity. Bioelectrical impedance analysis can measure changes in muscle and fat mass, while practical tests requiring a minimum

amount of equipment can measure changes in physical function (hand-grip dynamometry for strength, timed up-and-go for functional mobility, SPPB for overall physical function, 1-arm reach for dynamic balance), and the SF-36 questionnaire can measure quality of life. The detailed methodology is presented in the following chapter.

Chapter 4. Methods: A cross-sectional assessment of body composition and a 16-week intervention programme combining a high-protein hypocaloric diet with a mixed exercise regimen for Scottish older adults with low muscle mass and high fat mass.

In this chapter the detailed methodology of the research study is presented. The first stage of the study included a screening test (one-off assessment) of community dwellers aged 65 years and older. The main purpose of the test (denoted as *Screening (Test 1)* in **Figure 4.1**) was to assess body composition and strength. Bioelectrical impedance analysis and handgrip dynamometry were the main tools used to measure fat/muscle mass and strength, respectively. The data collected from the screening test were used to determine the presence of sarcopenia, obesity and sarcopenic obesity. Furthermore, the screening sessions allowed the researcher to identify eligible participants for the intervention study. A brief outline of the intervention follows in the next two paragraphs, with more details presented in section 4.5.2 and 4.5.3.

Those participants who met the inclusion and exclusion criteria for a high percentage of body fat and a low amount of muscle mass during *Test 1*, were allocated to an exercise-only group (EX; control) or an exercise and diet group (EXD; intervention). The duration of the intervention programme was 16 weeks and involved group exercise classes of low to moderate intensity (three classes weekly) combining different exercise modalities, which were the same for both groups. The diet in EXD provided a daily energy deficit (≤ 500 kcal) and a high protein intake relative to participants' bodyweight ($1.2 - 1.5$ g protein \cdot kg bw⁻¹ \cdot day⁻¹). A commercially available milk-based oral supplement rich in protein content (50 g milk protein per 500 mL serving) was administered once daily to assist the EXD group achieve the desired protein intakes. All participants received supplemental Vitamin D₃ (25 μ g three times weekly) regardless of their

group allocation. The primary outcomes (body composition, strength and function) were assessed at baseline, week 10 and end of week 16, whereas secondary outcomes such as dietary intakes and health related quality of life were assessed at baseline and at the end of week 16.

It is important to note here that the initial plan included the delivery of a 20-week intervention study with measurements taken at baseline, week 10 and week 20. However, due to methodological challenges (slow recruitment phase and hesitation of participants to commit to a 20-week programme), this was amended to a 16-week programme. When that decision was taken, two participants had already successfully completed 10 weeks of the programme and therefore had already undergone all measurements as per initial plan (at baseline and week 10). As a result, it was decided to keep the same time-plan for the first 10 weeks, with all measurements taken at baseline, week 10 and week 16 to ensure that all participants received the same treatment and were assessed at the same time points. Moreover, the inclusion criterion for sarcopenia was initially low skeletal muscle index combined with low strength, however, this criterion was amended to low muscle mass only, in order to improve recruitment rates for the intervention. This amendment occurred at the same time point as the change in total study duration (i.e. from 20 weeks to 16). The challenges related to the methodological design and implications will be discussed in detail in Chapter 8.

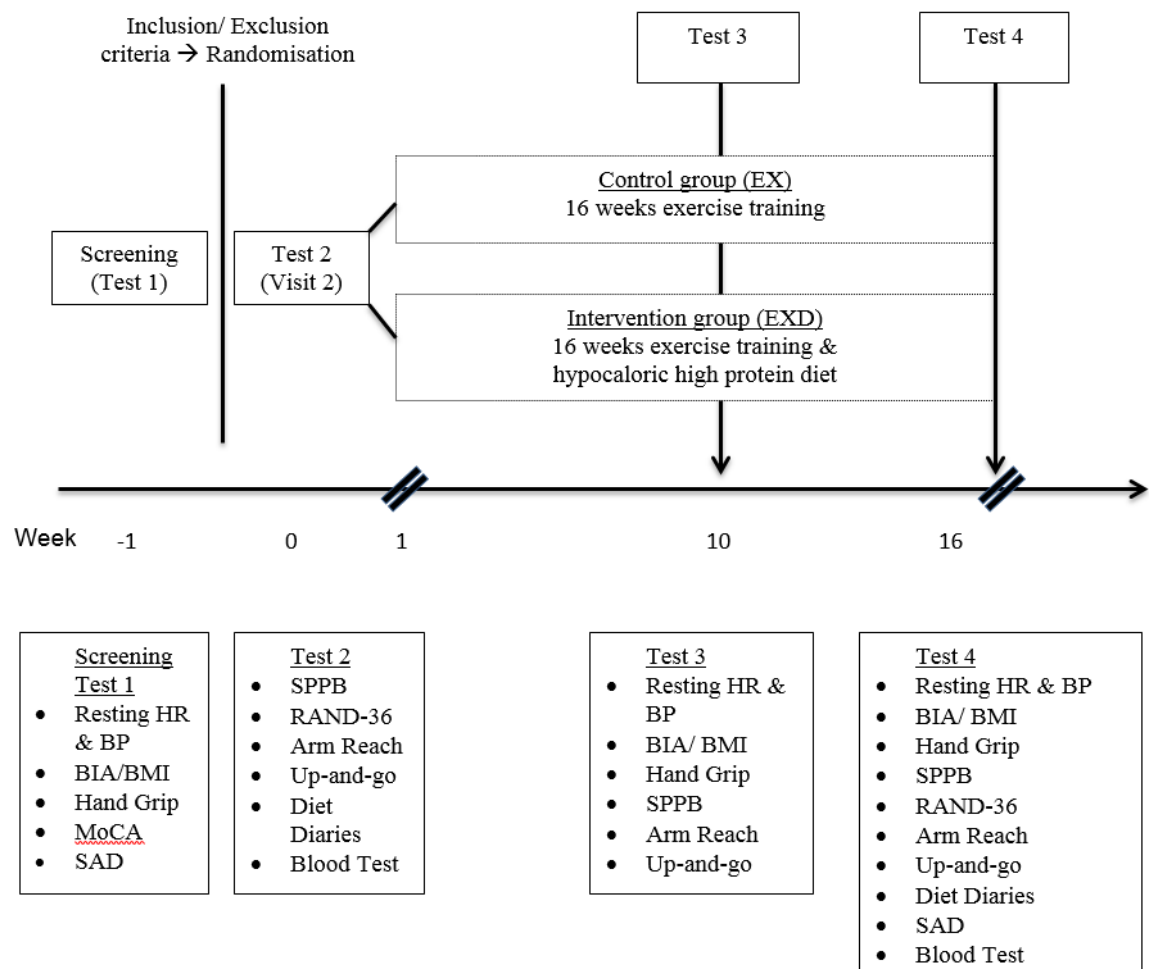


Figure 4.1 Study timeline and testing protocol. BIA: Bioelectrical Impedance Analysis, BMI: Body Mass Index, BP: Blood Pressure, HR: Heart Rate, MoCA: Montreal Cognitive Assessment, SAD: Sagittal Adipose Diameter, SPPB: Short Physical Performance Battery test. Week-1 assessments were conducted on any day of the two weeks preceding the initiation of the 16-week programme, whereas week 0 was a day of the week preceding week-1.

4.1 Population Characteristics - Inclusion and Exclusion criteria

Independent-living community dwelling adults from Lothian, Scotland, aged 65 years or older, and without a pacemaker, were eligible to participate in the screening visit. The exclusion of pacemaker-users was communicated to potential participants via email/phone enquiries and in the

study's information sheet, so that potential participants with pacemakers were informed before visiting the research premises. Eligible participants for the intervention study needed to have the physical, psychological and cognitive capacity to follow simple dietary plans/ advice and participate in regular and structured group exercise classes. The specific inclusion cut-offs for the intervention study were i) age ≥ 65 years, ii) percent body fat (%BF) $\geq 28\%$ in men and $\geq 40\%$ in women (Baumgartner et al. 2004), (iii) skeletal muscle index (SMI) $\leq 10.75 \text{ kg m}^{-2}$ in men and $\leq 6.75 \text{ kg m}^{-2}$ in women, and (iv) score ≥ 26 out of 30 in the cognitive assessment test (see section 4.5.1.5 *Cognitive Assessment Test*). The SMI cut-offs were based on the cut-offs published by the European Working Group on Sarcopenia in Older People (EWGSOP; the cut off scores are presented in more detail in the following section 4.5.1.1 *Assessment of sarcopenic obesity*) (Cruz-Jentoft et al. 2010). Initially, a low handgrip strength score was also used as an inclusion criterion ($< 20 \text{ kg}$ in women, and $< 30 \text{ kg}$ in men; Laurentani et al. 2003) however, this was later amended to allow for a greater number of participants in the study due to slow recruitment rates (discussed further in *Chapter 8*).

Exclusion criteria for the intervention study included self reported lactose intolerance, Parkinson's disease, uncontrolled pain, severe osteoporosis or arthritis, use of corticosteroids, history of pulmonary embolus or myocardial infarction within the previous two years, heart disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension (resting systolic pressure $>200\text{mmHg}$ or resting diastolic $>100\text{mmHg}$), acute systemic illnesses or any other uncontrolled physical, psychological, mental or cognitive impairment that would either prohibit adherence to the study protocol or would significantly increase health risks for participants.

4.2 Recruitment

Printed material was distributed to potential participants and community groups in the greater area of Lothian and in particular, Edinburgh, Musselburgh, Haddington, Dunbar and North Berwick. Posters, leaflets and information sheets providing details about the study were distributed at places commonly visited by older individuals. Public libraries, community settings, local markets, social events and exhibitions for older people were mainly targeted for recruitment. The researcher booked an exhibitor's stall at three separate events for older people in order to advertise the project and attract further public attention. Namely, the 'Spring Fling 2015', 'Mix & Mingle 2015' and 'Live Well in Later Life 2015' fairs were attended. Moreover, announcements were placed in local newspapers, community newsletters, social media and internet websites in the form of a press release, adhering to QMU research recruitment guidelines. Additional contact was made with the following organisations for recruitment purposes: the 'Ageing Well' association in East Lothian and Edinburgh, the 'University of 3rd Age', 'Age Scotland', 'Generations Working Together', 'Community connect', 'Changes', 'Edinburgh Health Forum', 'East Lothian Community Care Forum', 'Living it up', the 'Hollies' Day Centre in Musselburgh and the Rotary clubs in Musselburgh and Haddington.

4.3 Study Design

The first part of the study included a cross-sectional assessment of body composition and strength in older Scottish adults (Screening / Test 1; **Figure 4.1**). Older adults aged 65 years or older were invited to visit the research labs via recruitment strategies, as explained in more detail in section 4.2. That screening test involved a single session for each participant and took place at Queen Margaret University. The tests conducted during the screening visit were used to assess prevalence

of low strength (dynapenia), low strength combined with low muscle mass (sarcopenia), obesity (high %BF) and sarcopenic obesity, and to identify participants for the intervention study.

The intervention study was a randomised control trial (RCT) that took place at Queen Margaret University, (QMU) Edinburgh. Eligibility of the study participants was based on the results obtained during the screening test (**Figure 4.1**). If eligibility was confirmed, participants were allocated into either an exercise only group (EX), acting as a control, or an exercise and diet (EXD) group (intervention group). The two groups were stratified for sex and age (<75y and \geq 75y). Stratification was achieved by the method of minimisation (Altman and Bland 2005), using a Microsoft Excel spreadsheet and an allocation algorithm designed by a statistician independent of the study. For minimisation purposes, a 75% element of chance was implemented. That is, every new participant had a 75% chance of being allocated into that group that would minimise the imbalances in group sizes and characteristics (in order to stratify for age and sex). When the total number of participants in the groups was the same (e.g. when the very first participant enrolled and all group sizes were equal to zero), the allocation was done based on a 50% chance of being allocated to either of the groups.

4.4 Ethical approval

This study was conducted in accordance with the Declaration of Helsinki '*Ethical Principles for Medical Research Involving Human Subjects*' (World Medical Association 2013) and ethical approval was granted by the local (QMU) Research Ethics Committee (REC). Information sheets detailing the necessary information about the nature of the study were handed out to participants at least 24 hours prior to obtaining written consent. Written consent was then obtained by all

participants, however, participants were free to withdraw from the study at any time without the need to provide justification.

All data were anonymised and kept in a secure location, according to the Data Protection Act (1998) and the local QMU policy. The contact details of individuals were separated from the rest of the data and were securely stored in a separate locked cabinet to ensure that none of the sensitive data related to this study could be identifiable and traceable. All collected data were also duplicated in an electronic form (with no traceable contact details) and were stored in a password-protected computer. The data collection commenced in October 2014 and was completed in May 2016.

4.5 Outcome Measures

4.5.1 Screening (Test 1, observational data)

4.5.1.1 Assessment of sarcopenic obesity

The criteria proposed by the EWGSOP were used for the classification of participants with low muscle mass based on low skeletal mass index (SMI; skeletal muscle mass over squared height). Obesity was not identified based on body mass index (BMI) but by percent body fat (%BF). The cut-offs were sex-dependent. Namely, the cut-off for obesity in men was $\geq 28\%$, whereas in women $\geq 40\%$ (Baumgartner et al. 2004). The %BF values were derived directly from the BIA device.

Nevertheless, the BMI of participants was measured and is presented in *Chapter 6*. The BMI cut-offs are underweight: $\text{BMI} < 18.5$; normal: $18.5 \leq \text{BMI} \leq 24.99$; overweight: $25.0 \leq \text{BMI} \leq 29.99$;

Class I obesity: $30.0 \leq \text{BMI} \leq 34.99$; Class II obesity $35.0 \leq \text{BMI} \leq 39.99$; Class III obesity: $\text{BMI} \geq 40 \text{ kg m}^{-2}$.

Height was measured using a portable stadiometer (Seca 217 Stable Stadiometer, Seca, Birmingham, UK) after a maximum inhalation to the nearest 0.1 cm, and weight by a calibrated digital weighing scale (Seca 875 Class III, Seca, Birmingham, UK) to the nearest 0.1 kg, after shoes and heavy clothing were removed (International Society for the Advancement of Kinanthropometry 2001). Participants were asked to wear light and comfortable clothing that would not restrict movement on the assessment days.

BIA

Skeletal muscle mass (SMM), SMI and %BF were assessed using a dual-frequency (5 and 50Hz) Bioelectrical Impedance Analysis device (BodyStat 1500MDD, Bodystat ltd, Isle of Man, British Isles). Participants were asked to remove clothing with metal appurtenances and jewellery as well as their right sock (or stockings/tights) and lie in a supine position for five minutes prior to the test (Cote et al. 2014). They were asked to refrain from alcohol consumption, use of sauna and rigorous exercise 24 h prior to their visit. All BIA tests were performed in the morning, at approximately the same time for each participant ~ 9-11 am. The testing procedure for the assessment of body composition was performed according to the manufacturer's guidelines.

The equation used to calculate skeletal muscle mass (SMM) was that of Janssen et al. (2000);

$$\text{SMM (kg)} = [(\text{height}^2/\text{R} \times 0.401) + (\text{sex} * 3.825) + (\text{age} \times -0.0710)] + 5.102$$

where height is measured in centimetres, R is the resistance in Ohms, age in years and sex: women = 0 and men = 1. Skeletal muscle index (SMI) was derived from the formula $SMI = SMM \cdot \text{height}^{-2}$ ($\text{kg} \cdot \text{m}^{-2}$). Sarcopenia was indicated by a $SMI \leq 10.75 \text{ kg} \cdot \text{m}^{-2}$ in men and $\leq 6.75 \text{ kg} \cdot \text{m}^{-2}$ in women (Janssen et al. 2004).

4.5.1.2 Sagittal Abdominal Diameter

Sagittal abdominal diameter (SAD) was measured to the nearest millimetre using large sliding calipers (Rosscraft, Surrey, Canada) with the participant adopting a relaxed standing position with a normal breathing pattern and the arms folded across the chest. After following two normal breathing circles of the participant, the researcher took the measurement at end-tidal expiration. The measurement was taken horizontally at the site of the abdomen with the maximum anterior extension, inferior to the umbilicus. If however, the level of umbilicus was lower than the 5th lumbar spinal process, then the measurement was taken starting from the base of the lumbar spinous process presenting the greatest curvature to the corresponding point of the abdomen (the full protocol has been presented previously by Marfell-Jones et al. 2012).

4.5.1.3 Handgrip strength

A hydraulic handheld dynamometer (Takei 5001, Niigata City, Japan) was used to measure maximum hand grip strength to the nearest 0.5 kg. Participants were asked to press the dynamometer with the dominant hand and were encouraged to keep pressing it for 3-5 seconds as forcefully as possible with the elbow flexed at a 90° angle (Cote et al. 2014). That action was performed for a total of three times with a 30-sec rest period between the trials. All values were recorded but only the maximum value was used in further analysis. The hand grip strength

assessment was based on a standardised protocol recommended by Roberts et al. (2011). Although a handgrip score of <20 kg and <30 kg, in women and men, respectively, would denote low strength (i.e. dynapenia), handgrip strength was not used as an inclusion criterion for the intervention study.

4.5.1.4 Blood pressure and heart rate

Blood pressure and resting heart rate were measured using an electronic monitor (OMRON MX2, Omron Corporation, Kyoto, Japan) on the left arm after a 15 min rest (Tang et al. 2013). A 3-minute interval was allowed between each successive measurement according to the manufacturer's guidelines (Omron 2004), for a total of 3 measurements.

All anthropometrical tests (height, weight, SAD) as well as blood pressure and heart rate measurements were taken in triplicate and the mean values were used for analysis. All the aforementioned variables were measured in the morning and tests took place on a day of week -1 (**figure 4.1**), and subsequently for those who took part in the intervention study in week 10, and finally upon completion of the 16-week period (**figure 4.1**).

4.5.1.5 Cognitive Assessment Test

A cognitive status assessment was conducted only once, as a screening test before the start of the intervention trial to identify participants who scored below the cut-offs for normal cognitive function (Malafarina et al. 2013). The test used was the Montreal Cognitive Assessment (MoCA© Version 7.3) developed by Nasreddine et al. (2005). The test includes 11 questions and takes

approximately 10 minutes to complete. It assesses several domains of cognitive function including memory, concentration and attention, vigilance, orientation, executive functions and conceptual thinking. The maximum score that can be achieved is 30 and the cut-off value for inclusion in the present study was ≥ 26 , which is indicative of normal cognitive function according to the developers of the test (Nasreddine et al. 2005).

4.5.2 Randomised Control Trial: Test 2, 3 and 4.

The second visit (*test 2*, **Figure 4.1**) was attended only by those who met the criteria for participation in the RCT study. During *test 2* physical function, quality of life, and dietary patterns were assessed, and blood samples collected. All tests conducted during *test 1 and 2* were repeated following the same exact methodology in week 10 (*test 3*) and at the end of programme (*test 4*), with the exception of the cognitive test, the dietary assessment, quality of life and blood collections. The cognitive test was performed only at baseline, and the remaining three were performed at baseline and at the end of week-16 (**Figure 4.1**).

4.5.2.1 Short Physical Performance Battery (SPPB)

Physical performance was assessed using the Short Physical Performance Battery test (SPPB; Guralnik et al. 1994). The three components of the SPPB are 1) balance, 2) gait speed and 3) five repeated chair stands. The tests were always performed in this order. The maximum score for each of the tests was four points, with 12 points being the maximum score for the overall test. If a particular test could not be performed then the score achieved for that test was zero. A full copy of the detailed protocol guidelines and operationalisation has been previously published by Shumway-Cook and Woollacott (2007).

The balance test involved three different variations, the side by side stance, the semi-tandem and the full-tandem stance, trying to maintain each position for 10 or more seconds without making any steps or losing their balance. The researcher would initially demonstrate each position and if needed he would support the participants to adopt the required stance until they were confident they could independently maintain the position. The balance test was performed only once.

For the walking speed test, participants were asked to walk at their normal walking pace for a straight predesignated course. Two marks were placed on the floor eight ft (2.44 m) apart from each other. Participants would start from a standing position behind the first mark and were instructed to walk past the second mark. This was done to ensure that participants maintained a steady speed throughout the course without slowing down before reaching the second mark. A stopwatch was used to record the time. The timing would start upon the participant's first step and would stop when the participant's foot would land on the floor after the second mark. The instructions participants were given were '*I want you to walk at your normal walking pace, imagine that you walk down the road to go to a store*' and '*when you are ready you will start walking from this mark until you have walked past the final mark*'. They were allowed to use a walking aid if needed. They performed the test twice and the faster of the two was used for further analysis. Before the actual recording of the test they were instructed to walk up and down the room three times at their usual speed.

The third and final task tested ability to rise from a straight-backed chair for five consecutive times in the quickest possible time. They were not allowed to use their arms to rise; instead they were instructed to fold their arms across the chest. After they had received a demonstration from the

researcher, they were asked to perform one repetition with correct form to ensure that they were able to get up from the chair unassisted and to familiarise themselves with the task. If they were able to perform that, after a 30sec break they were asked to complete five chair stands as fast as possible maintaining the same stance with the arms folded across the chest.

4.5.2.2 Dynamic Balance

The 1-arm functional reach test was developed by Duncan et al. (1990) to assess dynamic balance and the full protocol has been described previously (Duncan et al. 1990; Rehabilitation Measures Database 2010). Participants were asked to adopt a comfortable upright stance with their right shoulder perpendicular to a wall (but without touching it) and their feet shoulder-width apart. A tape was then fixed on the wall at the participant's acromion height and parallel to the floor. Participants were instructed to raise their right arm until it is parallel to the tape (with their shoulder flexed at 90°), and close their fist so that the assessor could record the position of the 3rd metacarpal on the tape. Following this, the assessor instructed them to reach as far forward as comfortably possible keeping their right fist closed and next to the wall-affixed tape, without making a step or losing their balance. The final position of the 3rd metacarpal was recorded again. The distance covered between the initial and end position of the 3rd metacarpal was recorded in cm (Duncan et al. 1990; Kage et al. 2009) (**Appendix 4.3**). This was repeated 3 times, with a 1-min break between the trials. The mean value of the three attempts was calculated and used for analysis.

4.5.2.3 Functional Mobility

A timed get-up-and-go 6-m test was used to measure functional mobility. Participants were seated on a chair and on the command 'go' they tried to cover as fast as possible a pre-designated straight

distance of 3 meters and return back to the chair to adopt their initial seated position. The timing started on the command ‘go’ and was terminated when the back of the participant was in contact with the chair as described in more detail by Ramsbottom et al. (2004). The task was first demonstrated by the assessor and then the participants performed the test three times with one minute break in between the trials. The fastest time was recorded.

4.5.2.4 Muscle quality

Although muscle quality has been defined as muscle strength per unit of muscle mass, a single definition and diagnostic criterion has not been established yet (McGregor et al. 2014). In this study the definition of muscle quality was based on the operational criterion as presented by Barbat-Artigas et al. (2012), which is, handgrip strength measured by hand dynamometry (as described in 4.5.1.3) divided by skeletal muscle mass (calculated based on the BIA-derived equation by Janssen et al. (2004) as described in section 4.5.1.1).

4.5.2.5 Quality of Life (Rand 36/ SF-36)

Health related quality of life (HRQoL) was assessed using RAND-36/SF-36 questionnaire (RAND 2014). Participants were asked to complete the questionnaire on two occasions; the first was before the commencement of the intervention and the second upon the completion of the project (**Figure 4.1**). The scoring of the questionnaire was done according to the guidelines as detailed in the official website of the RAND Corporation (RAND 2014).

4.5.2.6 Collection and Storage of Blood Samples

Blood samples were taken at baseline at week-0 and after the completion of the 16-week period (**Figure 4.1**). The researcher was trained according to the NHS procedures in adult phlebotomy. The blood was taken from the superficial veins of the arm, namely the cephalic, basilic or median cubital veins. A single-use safety butterfly 21 or 23 gauge needle and a single use VACUETTE® collection tube were used for the collection of the blood samples. Immediately after each sampling the needle was safely discarded in a sharps bin. Blood was collected into Serum Gel-coated red tubes and was left at room temperature for 30-60 minutes in order to coagulate, according to the 'Standard Operating Procedures for Serum and Plasma Collection' published by Tuck et al. (2009). The room temperature, as well as the time period from collection to centrifugation, were recorded for every blood sample. The blood samples were centrifuged at 3000 RPM at 4°C for 10 minutes to separate the serum from the other blood components (clotting factors and cells). Serum was extracted using a sterile pipette and was inserted in Eppendorf tubes. The tubes were stored in accordance with the standard operational procedures at -80°C in a QMU laboratory freezer.

The blood serum was collected by the primary researcher of the current study but analysed for high-sensitivity C-Reactive Protein (hsCRP; Immunospectrophotometry), blood urea [Enzymatic (urease)], creatinine (Enzymatic), Insulin-like Growth Factor-1 (IGF-1; Chemiluminescent immunoassay), alkaline phosphatase [ALP; Enzymatic (para-nitrophenyl phosphate)], thyroid stimulating hormone (TSH; Chemiluminescent immunoassay), and 25(OH)D (Liquid chromatography tandem mass spectrometry LC-MS/MS) by the NHS Greater Glasgow and Clyde (NHSGGC) Specialist Endocrine Laboratory.

4.5.2.7 Assessment of dietary intake, analysis, and estimation of energy needs

Both groups were instructed to record their food intake for two weekdays and one weekend day to ensure that habitual intake was accurately recorded for a total of three days (week preceding the initiation of the exercise programme, denoted as week 0 in **Figure 4.1**). The 3-day diet diaries have been found to be reliable and valid in older populations free of cognitive impairments (Luhmann et al. 1999). The diet diaries were collected twice. The first one was obtained before the initiation of the 16-week programme and the second during the last week (16th) of the programme. Written and oral advice were given to all participants about diet recording techniques and how to estimate and report the portion sizes of the consumed meals in terms of common household measures (Appendix 4.2). When participants had difficulties estimating and reporting their food portions, the photographic food atlas was used (Nelson 2002) to quantify the portions consumed. The researcher reviewed the recorded diet diaries, and if anything was unclear or missing, participants were asked to provide further clarification. Dietary analysis to estimate energy and nutrient intakes was done with the use of the commercially available dietary analysis software, Nutritics (Nutritics Limited, Dublin, Ireland).

To estimate energy requirements in the EXD group, the basal metabolic rate (BMR) was estimated using the age and sex-specific Oxford equations produced by Henry (2005) and was multiplied by an individual physical activity level (PAL) factor (self reported by each participant) to calculate the estimated energy requirements (EER). Five hundred calories were subtracted from EER to produce a daily energy deficit that would allow for weight loss of approximately 0.45 kg (1.0 lbs) · week⁻¹. An example of the calculations can be found in Appendix 4.3. It was expected that a

daily deficit of 500 kcal would result in a maximum loss of approximately 7.2 kg (16 lbs) of body weight over the 16-week intervention period.

4.5.3 Intervention study protocol

4.5.3.1 Diet and supplementation protocol

The protein content of the diet (including the supplemental protein) was designed to achieve a protein intake of 1.2- 1.5 g · kg bw⁻¹, which translates to approximately 25 - 30% of the daily energy intake (Josse 2011; Tang et al. 2013). The post-workout liquid supplement provided 50 g of protein, which was consumed outside the main meals and counted towards the targeted energy intake and relative protein intake. The contribution of dietary fats to the daily total energy intake (TEI) was estimated at 25-30%, and the remaining energy requirements were provided by carbohydrates (~40-45% TEI).

Based on the desired relative proportions of energy derived from the different macronutrients and on the dietary preferences of the participants a diet plan was designed and given to each participant in EXD, using portion sizes/ servings in familiar units, (such as piece, spoonful, cup, or where necessary a metric amount was used, e.g. grams). Diet plans were aiming to include at least five portions of fruits and vegetables, minimise free sugar intake and consumption of processed foods. Vitamin D intakes were aided by the vitamin D supplement. An example diet plan can be found in **Appendix 4.4**. Alternative options with foods containing similar amounts of macronutrients were given based on lists of food exchange lists published elsewhere (Thomas and Bishop 2007; Josse 2011).

The protein-rich milk supplement was Promilk50 (Myprotein©, The Hut Group Ltd, Northwick, UK). The nutritional breakdown is presented in **Table 4.1** and the full amino acid profile in **Appendix 4.5**. Participants in the EXD group consumed one 500 mL bottle of milk supplement daily. On the exercise days they were instructed to consume one full serving after the workout. On non-exercising days they were encouraged to consume the supplement as a pre-sleep meal. A vitamin D3 tablet (Vitamin D, Sainsbury's Ltd, London, UK) of 25 µg was administered three times a week for a weekly total of 75 µg. To monitor adherence to the diet/supplementation protocol all participants were given a notebook to note their supplement and vitamin intake (those in the EX group received only the vitamin D tablets) (example in **Appendix 4.6**). The supplements were given to the participants every other week with sufficient amounts provided to cover the subsequent two weeks of the programme. During the delivery of the protein/vitamin supplements, the participants had a short discussion with the researcher to address compliance and any potential issues with the dietary and/or supplementation protocol. Participants were given oral and written guidelines for a healthy diet (**Appendix 4.7**). If any deviations or concerns were raised from participants, adjustments were made to ensure that participants adhered to the protocol. For example, if participants found it difficult to comply with the portion sizes, they were advised to increase the portion of the salad/vegetables (**Appendix 4.7**). If participants wanted to consume foods that were not in the initial diet plans (e.g. alcoholic beverages) allowances were made without compromising the overall diet plan (**Appendix 4.7**).

Table 4.1 Nutritional Information of the milk-based supplement (Promilk 50).

	Per 100ml	Per Bottle (500ml)
Energy	64 kcal/ 270 kJ	320 kcal /1350 kJ
Fat	0.2 g	1.0 g
of which saturates	0.1 g	0.5 g
Carbohydrate	5.2 g	26 g
of which sugars	5.1 g	26 g
Protein	10.1 g	50.5 g
Salt	0.14 g	0.7 g

Notes: Milk ingredients: Skimmed Milk, Milk Protein, Butter Milk Powder (*or* Fat-Reduced Cocoa Powder in the case of Chocolate flavour), Flavourings, Thickener (E407), Sweetener (E955).

4.5.3.2 Exercise

The exercise classes combined simple existing exercise protocols that have been tailored towards older adults and are practical and affordable enough to be used again in the future. The exercise sessions included resistance, balance, aerobic and flexibility elements. The resistance element aimed to promote strength, function and hypertrophy, the aerobic for its cardiovascular benefits, the balance in order to challenge and improve postural stability, and lastly flexibility in order to maintain healthy joints engaging at a functional range of movement.

The difficulty and complexity of the exercises was planned to increase progressively over time. Participants trained under constant supervision in small groups of up to five people and the classes took place three times per week on non-consecutive days (e.g. Monday-Wednesday-Friday). Only the absolute necessary pieces of equipment were provided in the classroom, namely, chairs,

resistance exercise bands (Theraband®), and in some sessions wall mirrors. The sessions took place at Queen Margaret University Sports Centre in studios dedicated to drama, dancing and other group sessions and the duration of the exercise sessions was approximately one hour. The exercise programme followed a progressive loading and periodization structure but it was also tailored to individual abilities and tolerance. The researcher, personal trainer and fitness professional (member of the UK Register of Exercise Professionals), qualified in strength training for older people as well as in chair-based exercise classes for older adults, delivered and supervised all exercise sessions. The researcher was also trained to provide first aid and cardiopulmonary resuscitation (CPR) by the Royal Life Saving Society (RLSS) UK. In addition, at any time there were another two members of staff in the building able to provide first aid assistance. A semi-automatic defibrillator was clearly signposted and available for the first aiders.

An individual record sheet was used to register attendance frequency, injuries, adverse clinical events that could occur during the workout sessions or any other comments that the participants wished to make in regard to intensity, difficulty or the general nature of the programme.

Exercise Days

The main objective of the exercise programme was to improve muscle strength and/or function of the most important muscle groups responsible for maintaining good balance, posture and mobility. Therefore, exercises focusing on the back, chest, leg and trunk muscles were of primary interest. Particularly exercises that engaged the shoulder adductors/ abductors, hip adductors/ abductors and flexors/extensors, knee flexors/extensors and elbow flexors/extensors were performed (Lobo 2010; Williamson 2011; VanBeveren 2012) (**Appendix 4.8**).

Exercise sessions were performed in the morning, with at least 48 hours between each session. The exercise sessions lasted ~1 hour; the first 10 minutes were used for warm up and the last 10 min for stretching, cool down and recovery. The main body of the session (40 minutes) consisted of balance, seated and bodyweight exercises during the first two weeks. This allowed participants to familiarise themselves with the exercises and techniques, improve their proprioception, aerobic capacity and engage progressively the major muscle groups to minimise delayed onset muscle soreness (DOMS), which could potentially discourage participation in the study. The exercise instructor would give a detailed demonstration of how the exercises should be performed, placing particular emphasis to correct technique and posture as well as breathing patterns. When participants were performing the exercises they would receive instant and constructive feedback by the instructor, explaining whether the technique was correct and what could be improved, using simple terms and prompts.

The progressive resistance exercise training was based on the use of elastic bands (Theraband© Hygienic Co., Akron, OH) from week-3 and forward. These elastic bands offer different resistance levels depending on their thickness and colour. Namely, in an ascending order of thickness, the yellow, red, green, blue, black and silver bands, can produce a force of 1.32, 1.77, 2.27, 3.22, 4.40, and 5.99 kg, respectively, when elongated by 100% (Page and Ellenbecker 2011). Before initiating the exercise programme participants were asked whether they were allergic to latex, in which case latex-free elastic bands of the same resistance were available.

All participants started with the lightest band in week-3, i.e. the yellow colour band and were instructed to perform initially 8-12 repetitions of each exercise. The exercises were performed in a circuit pattern until all exercises had been executed for a total of three times. To avoid early fatigue due to the circuit pattern, upper and lower body (or opposing muscle groups) exercises were alternated. Between each exercise there was a ~15 sec break during which the instructor would demonstrate the next exercise, whereas in-between each circuit there was a 1-2 min break. In week-4 the same exercises were performed but the repetitions increased to 10-15. All exercises for legs, back and chest in the last circuit (3rd) were performed to volitional fatigue (i.e. to that point that participants were unable to perform an additional repetition, or at least were unable to perform it with a proper form). If participants were able to perform ≥ 15 repetitions, they were then allowed to progress to the next colour of bands the following week. Similarly in week 5, participants would start from 8-12 repetitions and would gradually increase to 10-15 until the end of the week 6, when they would perform the last sets to volitional fatigue to demonstrate an ability to progress to the higher resistance level. Therefore, every two weeks the participants could progress to the next level of resistance as presented in **table 4.2**.

During the first 14 weeks participants were encouraged to perform the exercises with the elastic bands in a controlled manner, concentrating more on technique and using the full range of motion, rather than speed of movement. Therefore both the concentric and eccentric phase of each movement would last ~1-2 secs, with a further 2 sec pause/rest between each phase. During the last two weeks (15-16) participants were instructed to increase the velocity of movement to ≤ 1 sec, but maintain a slow eccentric phase (≥ 2 sec). A 10-point Borg scale was used to monitor the participants' rate of perceived exertion during the exercise classes, during the breaks at the end of circuits. The instructor aimed to keep the intensity at moderate levels, that is, not surpassing a 6-

grade rating in the Borg scale (with the exception being the last circuit of the even weeks, where exercises were performed to volitional fatigue).

Table 4.2 Planned progression of resistance exercise training

Weeks		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Resistance	BW	X	X														
	Yellow			X	X												
	Red					X	X										
	Green							X	X								
	Blue									X	X						
	Black											X	X				
	Silver													X	X	X*	X*

Notes: BW, bodyweight. * The concentric part of the movement was increased to 'as fast as possible' and of the eccentric decreased to ~2 sec.

4.5.4 Sample Size calculation and statistical analysis

Sample size was calculated based on the primary outcome, which was change in skeletal muscle mass as estimated by dual-frequency BIA. The equation used to calculate sample size has been previously presented by Noordzij et al. 2010 (Appendix 4.9). With a statistical significance level set at 0.05, a power of 80%, a standard deviation of ± 1.4 kg (Siervo et al. 2012) and a 1.1 kg change needed to detect a significant difference between the groups (Borsheim et al. 2008), 18 participants per group would allow for such calculations. Considering a 25% drop out rate, a final sample size of 50 participants (25 per group) was required.

A Shapiro-Wilk test was used to assess the distribution (normality) of data. Non-normally distributed data were presented accordingly; that is, the measure of centrality with a median and that of dispersion with the interquartile range (IQR 25th, 75th). Similarly, associations between non-normally distributed variables were assessed using a Spearman's correlation test. A *Spearman's Rho* value between 0.1 and 0.3 indicated a weak association, 0.3 to 0.5 a moderate association, and ≥ 0.5 a strong association Cohen (1988). Statistical differences at baseline were assessed by Mann-Whitney U-test. A one-sample Wilcoxon signed-rank test was used to compare median (IQR) outcomes from the current cohort to known single values from the Scottish Health Survey (Scottish Government 2017) for body mass index, and from the national official statistics from the latest National Diet and Nutrition Survey (NDNS) (GOV UK 2018) for dietary intakes. A statistical package (SPSS version 19.0) was used for the statistical analysis.

4.5.5 Summary

On the first test day the objective was to assess body composition indices that would allow the researcher to evaluate how many adults ≥ 65 years had low strength (dynapenia), low muscle mass, low strength and low muscle mass (sarcopenia), obesity (based on BMI and %BF), and sarcopenic obesity. The second test day focused on measuring function, quality of life and dietary habits, for those who had been screened during the first test day and were found to be eligible for the intervention study (i.e. have low muscle and high fat mass). Participants were then allocated to either a control group (EX: exercise only) or intervention group (EXD: exercise and diet), and took part in a 16-week trial. All participants received a vitamin D supplement and performed the same exercise routine. Participants in EXD received an energy deficit diet (500 kcal less than their individual estimated energy requirements) on top of the exercise and the Vitamin D tablets, and were also supplemented with a milk based protein supplement to achieve the target of $1.2\text{-}1.5 \text{ g protein} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$. The results of all test days (observational data for the whole cohort, and the data from the intervention study at baseline, week 10 and week 16) are presented in the following chapters.

Chapter 5. Results: Sarcopenic obesity in Scottish older community-dwellers. A cross-sectional study.

The cohort characteristics from the screening session (cross-sectional study) are presented in this chapter. Due to a non-normal distribution of the main outcomes results are presented using median (IQR: 25th, 75th percentile) and Spearman's Rho values. Initially, 156 adults ≥ 65 years old responded to the advertisement and subsequently, 108 of them consented to take part in the screening test. Recruitment flow is presented in **Figure 5.1**, in agreement with the CONSORT guidelines.

Based on the BMI classification criterion, obese adults had a significantly higher skeletal muscle mass (SMM) than the non-obese. However, when obesity was defined as high % BF (≥ 28 % in men and ≥ 40 % in women), the opposite pattern was observed. That is, the non-obese had significantly higher SMM than the obese and additionally, the non-obese exhibited a higher handgrip (*section 5.1.1*). Overall prevalence of sarcopenia was 14.8 % (16/108) (*section 5.1.2*). The use of sex-specific %BF cut-offs identified more cases of obesity and sarcopenic obesity than the BMI cut-off of $\geq 30 \text{ kg}\cdot\text{m}^{-2}$. Namely, prevalence of obesity based on BMI was 27.8 % (30/108) vs 63.0 % (68/108) based on %BF, whereas prevalence of sarcopenic obesity was 4.6 % (5/108) based on BMI vs 12.0 % (13/108) based on %BF (*section 5.1.2*). Muscle quality (handgrip strength per unit of skeletal muscle mass) showed a significant and negative association with bodyweight, sagittal abdominal diameter (SAD) and absolute fat mass in men and women (*section 5.1.3*). More details are presented in the following sections.

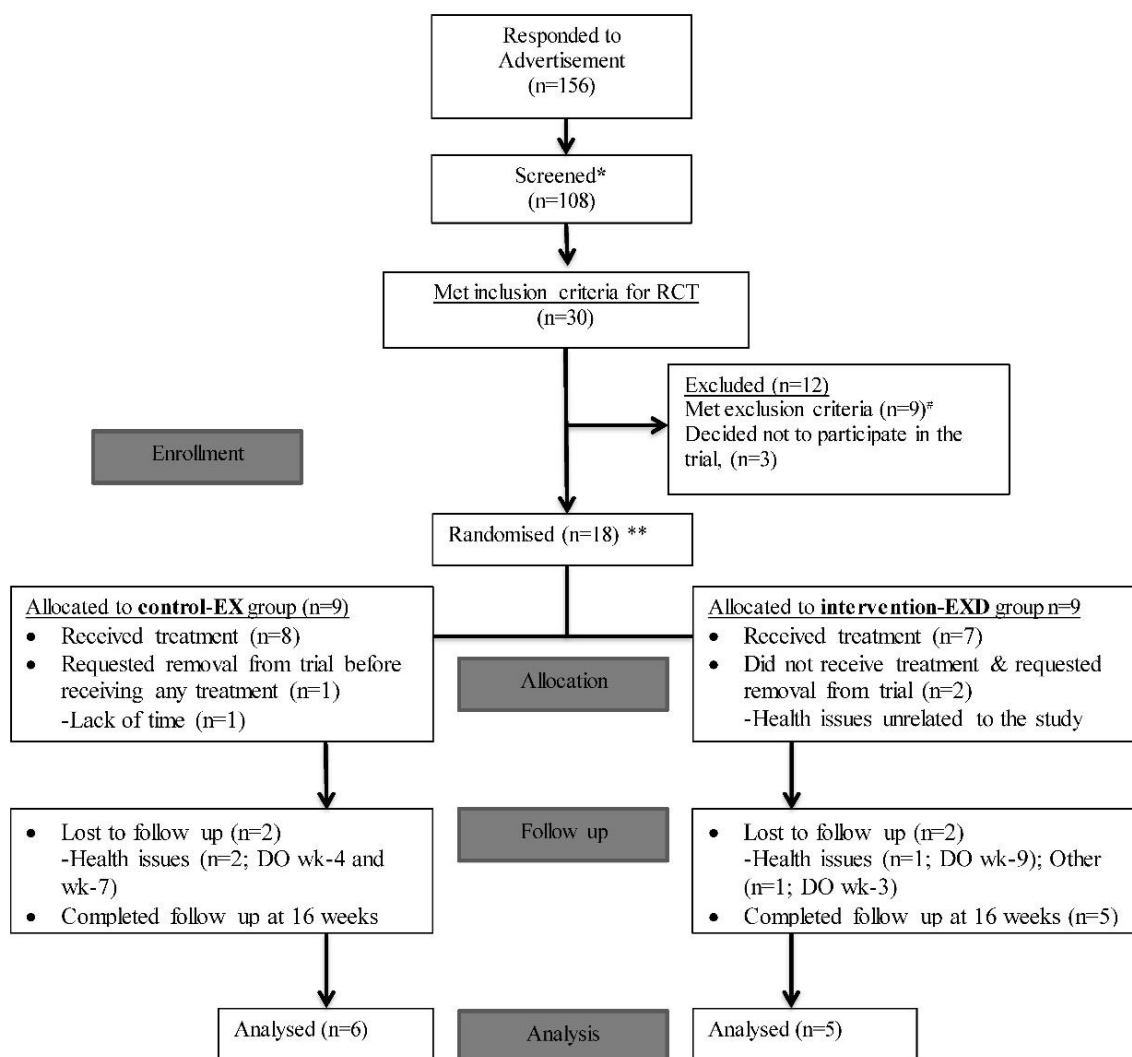


Figure 5.1 CONSORT recruitment flow. * cross-sectional data, presented in section 5.1 . ** RCT data are presented in Chapter 6. # Exclusion reasons are presented in *Section 6.3*. DO, drop-out.

5.1 Screening for sarcopenia, obesity and sarcopenic obesity in Scottish older adults (cross-sectional data)

5.1.1 Participant characteristics

One hundred and eight adults (men, n=29; women, n=79) took part in the screening visit, which involved undertaking the tests described in Chapter 4. Results are presented as median (IQR) values (**Table 5.1**). Overall, the median age of participants was 70 (67, 75) yr. Weight and BMI, were 73.8 (63.4, 86.3) kg and 26.9 (24.0, 31.0) kg·m⁻², respectively. Fat mass was 28.0 (22.2, 35.9) kg and % BF 40.3 (32.2, 45.6) %. Lean mass (LM) was 42.9 (37.3, 52.9) kg, skeletal muscle mass (SMM) 19.3 (17.1, 27.7) kg and skeletal muscle index (SMI) 7.44 (6.71, 9.28) kg m⁻². Handgrip strength and sagittal abdominal depth (SAD) were 25.0 (21.5, 31.5) kg and 27.3 (24.2, 31.0) cm, respectively (**Table 5.1**). Based on the BMI cut-offs 30 participants met the obesity criteria, whereas based on high % BF 68 participants were classified as obese (**Table 5.2**).

Differences between Scottish older men and women

Men were significantly younger than women, 67 (65, 73) yr vs 71 (68, 75) yr (p=0.003) and had a higher bodyweight, 85.6 (74.8, 97.5) kg vs 69.5 (61.4, 80.0) kg (p<0.001) (**Table 5.1**). Men had significantly higher % LM [73.1 (68.3, 75.3) % vs 57.7 (53.0, 60.8) % (p<0.001)], SMI [9.96 (9.34, 11.11) kg ·m⁻² vs 7.08 (6.42, 7.73) kg ·m⁻², (p<0.001)] and handgrip strength [42.5 (31.4, 46.5) kg vs 23.5 (20.5, 26.5) kg, p<0.001]. Women had significantly higher % BF [42.3 (39.2, 47.0) % vs 26.9 (24.7, 31.8) %, p<0.001] and ratio FM: SMM [1.6 (1.3-2.0) vs 0.7 (0.6-0.9) p<0.001] (**Table 5.1**). The BMI of men (27.1 kg m⁻²) and women (26.7 kg m⁻²) of this cohort was not significantly different to the national average BMI of Scottish men (29.7 kg m⁻²) (p=0.088)

and women (28.4 kg m^{-2}) ($p=0.195$) of a similar age group, 65-75 years (Scottish Government 2017).

Table 5.1 Baseline characteristics of men and women who participated in the screening session.

	Overall n=108		Men n=29		Women n=79		<i>p</i> (sig.) value
	Median	IQR	Median	IQR	Median	IQR	
Age (yr)	70	(67, 75)	67	(65, 73)	71	(68, 75)	0.003
Weight (kg)	73.8	(63.4, 86.3)	85.6	(74.8, 97.5)	69.5	(61.4, 80.0)	<0.001
Height (m)	1.63	(1.60, 1.69)	1.75	(1.72, 1.80)	1.61	(1.58, 1.64)	<0.001
BMI (kg m ⁻²)	26.9	(24.0, 31.0)	27.1	(24.2, 33.4)	26.7	(23.9, 31.4)	0.579
%BF	40.3	(32.2, 45.6)	26.9	(24.7, 31.8)	42.3	(39.2, 47.0)	<0.001
FM (kg)	28.0	(22.2, 35.9)	22.4	(18.9, 30.5)	28.6	(23.2, 36.5)	0.001
% LM	59.8	(54.5, 67.8)	73.1	(68.3, 75.3)	57.7	(53.0, 60.8)	<0.001
LM (kg)	42.9	(37.3, 52.9)	60.6	(56.3, 69.3)	40.6	(36.0, 44.3)	<0.001
SMM (kg)	19.3	(17.1, 27.7)	30.6	(29.2, 33.7)	18.5	(16.4, 20.1)	<0.001
SMI (kg m ⁻²)	7.44	(6.71, 9.28)	9.96	(9.34, 11.11)	7.08	(6.42, 7.73)	<0.001
FM:SMM	1.4	(1.0, 1.9)	0.7	(0.6, 0.9)	1.6	(1.3, 2.0)	<0.001
Handgrip (kg) ^I	25.0	(21.5, 31.5)	42.5	(31.4, 46.5)	23.5	(20.5, 26.5)	<0.001
Muscle Quality (HG:SMM) ^I	1.28	(1.06, 1.51)	1.37	(1.03, 1.49)	1.28	(1.08, 1.51)	0.792
SAD (mm) ^{II}	27.3	(24.2, 31.0)	28.3	(24.7, 33.5)	26.8	(23.3, 30.3)	0.048
SBP (mmHg) ^{III}	137	(127, 149)	134	(127, 150)	136	(127, 146)	0.823
DBP (mmHg) ^{III}	78	(71, 83)	75.5	(71, 82)	78	(71, 83)	0.910
HR ^{III}	68	(60, 74)	64	(57, 69)	70	(62, 76)	0.003

Notes: ^I n=105 (78f, 27m); ^{II} n=101 (74f, 27m); ^{III} n=107 (79f, 28m); %BF, percent body fat; BMI, body mass index; DBP, diastolic blood pressure; FM, fat mass; HR, heart rate; LM, lean mass; SAD, sagittal abdominal diameter; SBP, systolic blood pressure; SMI, skeletal muscle index; SMM, skeletal muscle mass.

Differences between obese vs non-obese older adults

Body mass index, % BF and absolute fat mass were significantly higher in the obese groups regardless of classification method (**Table 5.2**). Based on the BMI classification criterion, obese adults had a significantly higher skeletal muscle mass (SMM) than the non-obese [21.8 (19.1, 28.4) kg vs 18.7 (16.4, 26.7) kg] ($p=0.008$) (**Table 5.2**). Moreover, adults with obesity based on BMI had a significantly higher SMI than their non-obese counterparts [8.4 (7.47, 10.67) $\text{kg}\cdot\text{m}^{-2}$ vs 7.08 (6.42, 9.00) $\text{kg}\cdot\text{m}^{-2}$, $p<0.001$]. When obesity was defined as increased % BF, the opposite pattern was observed; the non-obese group had significantly higher SMM than the obese [21.1 (18.7, 23.5) kg vs 18.9 (16.4, 21.8) kg, $p=0.005$] and was also stronger [27.5 (24.5, 42.3) kg vs 24.5 (20.0, 21.8) kg, $p=0.001$]. Regardless of the classification criterion used, muscle quality was significantly lower in the obese vs the non-obese (**Table 5.2**).

Table 5.2 A comparison of body composition and strength indices between obese and non-obese Scottish older adults, based on two different classification methods, BMI and % body fat.

	BMI					%BF				
	Non-Obese n=78		Obese n=30		p (sig.)	Non-Obese n=40		Obese n=68		p (sig.)
	Median	(IQR)	Median	(IQR)		Median	(IQR)	Median	(IQR)	
Age (yr)	69	(66, 74)	71	(68, 76)	0.142	68	(66, 71)	73	(68, 77)	<0.001
BMI (kg m ⁻²)	25.5	(23.3, 27.1)	34.7	(32.7, 36.8)	<0.001	23.9	(22.6, 26.6)	29.4	(25.9, 34.5)	<0.001
%BF	38.4	(28.8, 42.3)	47.3	(40.0, 50.3)	<0.001	33.9	(26.1, 37.9)	43.7	(40.8, 48.8)	<0.001
FM (kg)	24.0	(20.9, 28.3)	40.0	(35.7, 47.3)	<0.001	21.4	(19.1, 22.8)	32.5	(28.0, 39.6)	<0.001
% LM	61.6	(57.5, 71.4)	52.0	(49.6, 60.2)	<0.001	66.4	(62.0, 74.1)	56.1	(51.2, 59.3)	<0.001
SMM (kg)	18.7	(16.4, 26.7)	21.8	(19.1, 28.4)	0.008	21.1	(18.7, 16.4)	18.9	(16.4, 21.8)	0.005
SMI (kg m ⁻²)	7.08	(6.42, 9.00)	8.4	(7.47, 10.67)	<0.001	7.84	(7.02, 9.52)	7.16	(6.53, 8.61)	0.060
Strength (kg)	25.0	(21.5, 31.8)	25.5	(21.5, 30.5)	0.681	27.5	(24.5, 42.3)	24.5	(20.0, 28.0)	0.001
Muscle Quality (ratio)	1.35	(1.16, 1.58)	1.11	(0.90, 1.31)	<0.001	1.39	(1.24, 1.55)	1.21	(1.02, 1.46)	0.036

Notes: %BF, percent body fat; %LM, percent lean mass; BMI, body mass index; FM, fat mass; HR, heart rate; Muscle Quality (handgrip: skeletal muscle mass); SMI, skeletal muscle index; SMM, skeletal muscle mass.

Outliers

Regarding outliers, one person produced consistently higher values than the rest of the cohort for BMI, body fat mass, SMM, and SMI and was detected as an outlier by the SPSS-derived boxplots (**Appendix 5**; participant no.44). This participant was a 69 years old woman who had the highest bodyweight of 127.6 kg, highest BMI (44.8 kg m^{-2}) and highest amount of absolute fat mass (FM: 67.5 kg) amongst the whole cohort, regardless of sex. Interestingly, the same participant exhibited the highest amounts of absolute lean mass (LM=60.1 kg) and muscle mass (SMM=28.4 kg), as well as one of the three highest SMIs (SMI=10.58 kg m^{-2}) amongst women. That person met the eligibility criteria for screening and there were no numerical errors or incorrect procedures during the assessment tests; moreover, in a larger sample size it is likely that this participant would not appear as an outlier. Therefore, all data from this participant were included in the analysis and presentation of the results.

5.1.2 Prevalence rates of low strength (dynapenia), low muscle mass, sarcopenia, underweight, overweight, obesity and sarcopenic obesity.

Low hand grip (dynapenia) characterised five men (17.2% of all men), 17 women (21.5% of all women) and 22 out of 108 (20.3%) participants in total (**Table 5.3**). A total of 18 out of 29 men (62.1%) were characterised by low skeletal muscle mass (SMM), whereas in women the respective figure was 39% (29 out of 79). In total, low SMM was present in 43.5% (47 out of 108) of participants. Prevalence of sarcopenia (i.e. those with low SMM combined with low handgrip strength) was 14.8% (16 out of 108) overall, with rates in men and women being 13.8% and 15.2%, respectively (**Table 5.3**).

Based on BMI classification, one person (n=1) was identified as underweight, 32 participants had a BMI within the normal range, and 45 participants were classed as overweight (**Table 5.4**). Thirty out of 108 (27.8%) were classified as obese based on $\text{BMI} \geq 30 \text{ kg m}^{-2}$. Out of those 30 participants with obesity, 17 were characterised by class I obesity, 11 by class II obesity and two by class III obesity (the full BMI classifications and cut-offs are presented in **Table 5.4**). Based on the gender-specific %BF cut-offs, 63.0% of all participants (68 out of 108) were classified as obese. Finally, when sarcopenia was combined with a high BMI, 4.6% (five out of 108) presented the sarcopenic obesity phenotype, compared with 12.0% (13 out of 108) who were characterised by sarcopenic obesity based on sarcopenia and high %BF. **Table 5.5** presents the different BMI categories (normal, overweight, obesity) corresponding to %BF values, in men and women. Overweight men and women had a median (IQR) % BF of 26.9 (24.7, 28.5) % and 42.1 (40.6, 45.8) %, respectively. Obese men and women had a median (IQR) % BF of 32.6 (31.7, 35.6) % and 49.4 (45.7, 52.4) %, respectively.

Table 5.3 Prevalence of low strength (dynapenia), low muscle mass, sarcopenia, obesity and sarcopenic obesity (based on high BMI and high %BF) in a cohort of 108 older (≥65 yr) Scottish dwellers.

	Men ¹	Women ²	All ³
	(%)	(%)	(% total)
Dynapenia	5 (17.2)	17 (21.5)	22 (20.3)
Low SMM	18 (62.1)	29 (36.7)	47 (43.5)
Sarcopenia ^a	4 (13.8)	12 (15.2)	16 (14.8)
Obesity by BMI	7 (24.1)	23 (29.1)	30 (27.8)
Obesity by %BF	12 (41.4)	56 (70.9)	68 (63.0)
Sarcopenic Obesity by BMI	0 (0)	5 (6.3)	5 (4.6)
Sarcopenic Obesity by %BF	2 (6.9)	11 (13.9)	13 (12.0)

¹n=29; ²n=79; ³n=108; ^a sarcopenia regardless of obesity; BMI, Body Mass Index; %BF, % body fat

Table 5.4 Overall and gender-specific BMI classifications of the whole cohort based on the WHO guidelines

Classification	BMI (kg m ⁻²) category range	Men ¹ (%)	Women ² (%)	All ³ (% total)
Underweight	BMI <18.5	0 (0)	1 (1.3)	1 (0.9)
Normal	18.5 ≤ BMI ≤ 24.99	8 (27.6)	24 (30.4)	32 (29.6)
Overweight	25.0 ≤ BMI ≤ 29.99	14 (48.3)	31 (39.2)	45 (41.7)
Class I	30.0 ≤ BMI ≤ 34.99	4 (13.8)	13 (16.5)	17 (15.7)
Class II	35.0 ≤ BMI ≤ 39.99	2 (6.9)	9 ()	11 (10.2)
Class III	BMI ≥ 40	1 (3.4)	1	2 (1.9)

¹n=29; ²n=79; ³n=108

Table 5.5 Percent body fat in the different BMI categories in men (n=29) and women (n=79).

BMI (kg m ⁻²)	Median %BF (IQR)	
(men n ¹ : women n ²)	Men	Women
≤ 18.49 (0: 1)	-	*
18.5-24.99 (8: 24)	24.7% (23.0, 26.4)	37.8% (34.2, 40.3)
25-29.99 (14: 31)	26.9% (24.7, 28.5)	42.1% (40.6, 45.8)
≥ 30 (7: 23)	32.6 % (31.7, 35.6)	49.4% (45.7, 52.4)

¹n=29; ²n=79; * One woman (n=1) had BMI < 18.5 kg m⁻², at a %BF of 41.5%

5.1.3 Relationship between age, body composition, and strength/function.

All associations are presented as *Spearman's Rho (rank correlation coefficient)* values. A moderate positive and significant association was observed between age and %BF (Rho=.45, $p<0.001$; **Figure 5.2**). A strong, significant and negative association was reported between age and handgrip strength (Rho=-0.63, $p<0.0001$; **Figure 5.2**). Handgrip strength was also strongly, significantly and positively associated with SMM (Rho=0.63, $p<0.001$; **Figure 5.2**), whereas it was significantly and negatively associated with %BF (Rho=-0.60, $p<0.001$; **Figure 5.3**) and FM: SMM ratio (Rho=-0.58, $p<0.001$; **Figure 5.3**).

Although a weight bearing exercise was not performed for the assessment of muscle quality (handgrip strength per unit of skeletal muscle mass), the latter showed a significant and negative association with bodyweight (Rho=-0.33, $p=0.001$), SAD (Rho=-0.40, $p<0.001$) (**Figure 5.4**) and absolute fat mass (Rho=-0.35, $p<0.001$) (**Figure 5.5**). All reported associations remained significant after a separate subgroup analysis for men and women (**Figure 5.5** presents the association between muscle quality and fat mass in men and women).

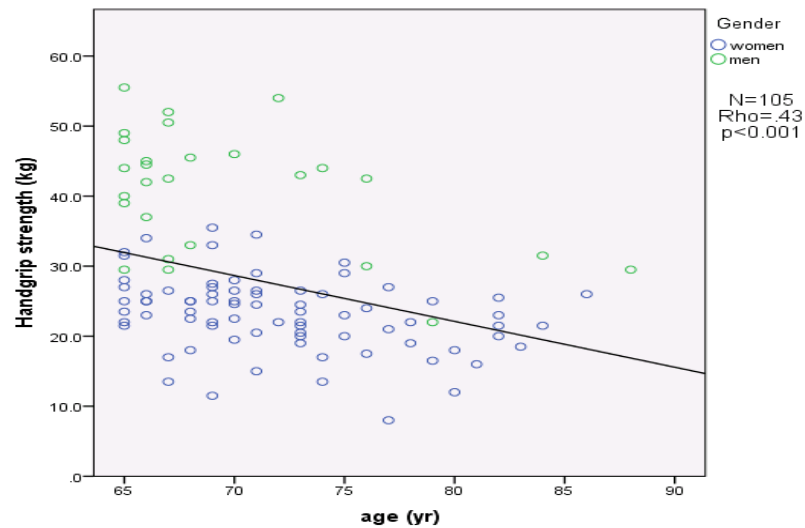
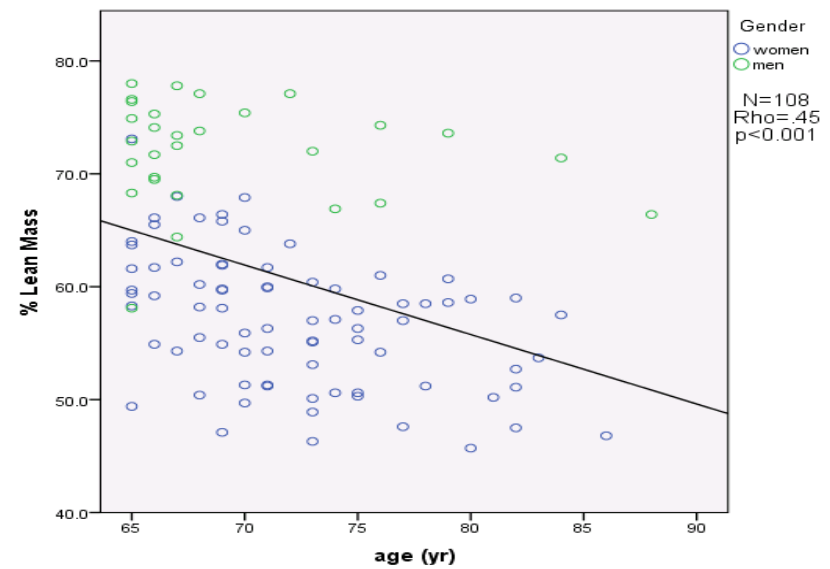
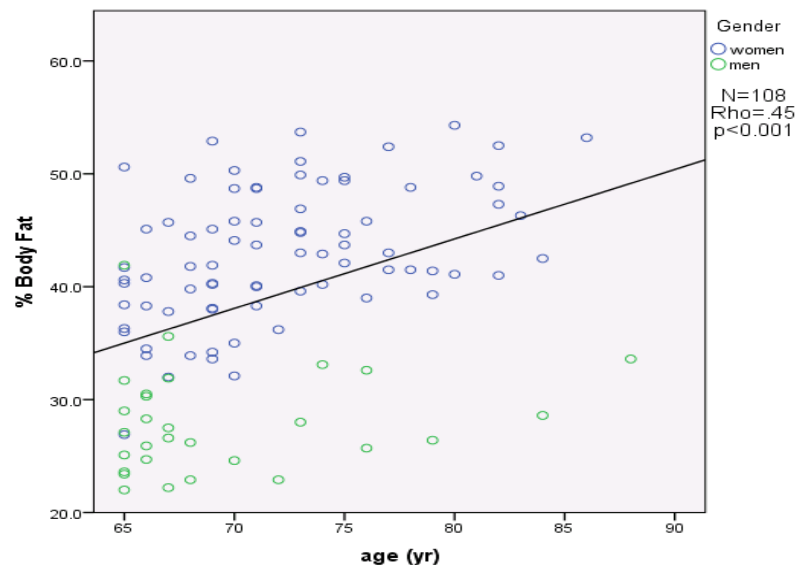


Figure 5.2 Association between %BF, %LM, and Handgrip with age. Top left: Association between % body fat and age (yr). Top right: Association between % lean mass and age (yr). Bottom left: Association between handgrip strength (kg) and age (yr).

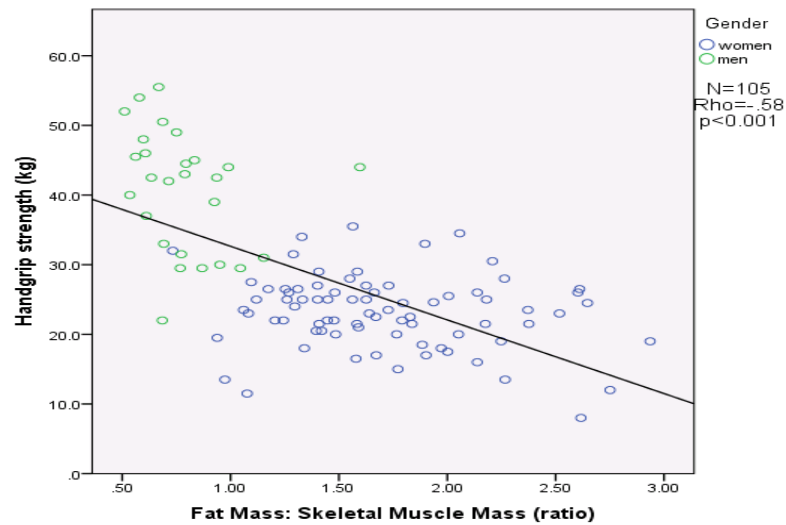
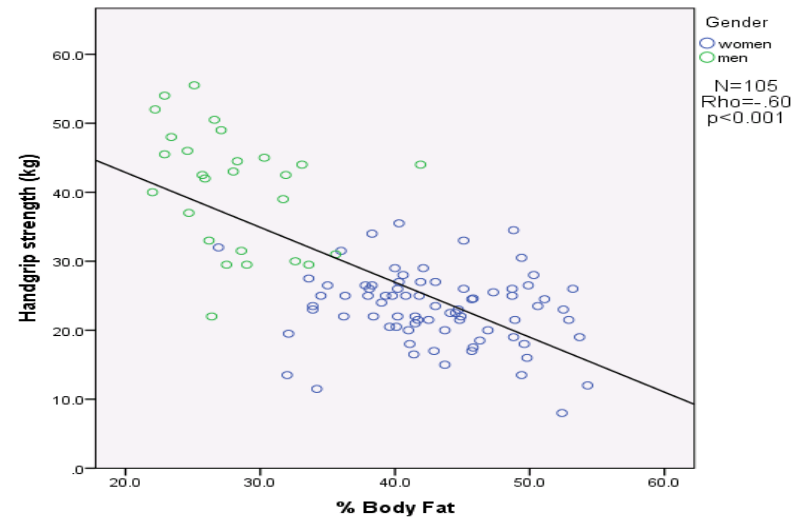
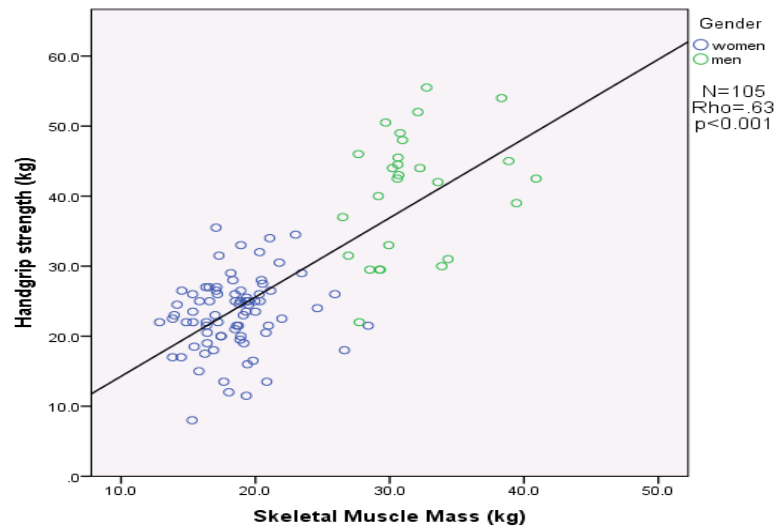


Figure 5.3 Association between handgrip with SMM, %BF and FM:SMM. Top left: Association between handgrip (kg) and skeletal muscle mass (kg). Top right: Association between handgrip (kg) and % body fat. Bottom left: Association between handgrip and ratio of fat mass: skeletal muscle mass.

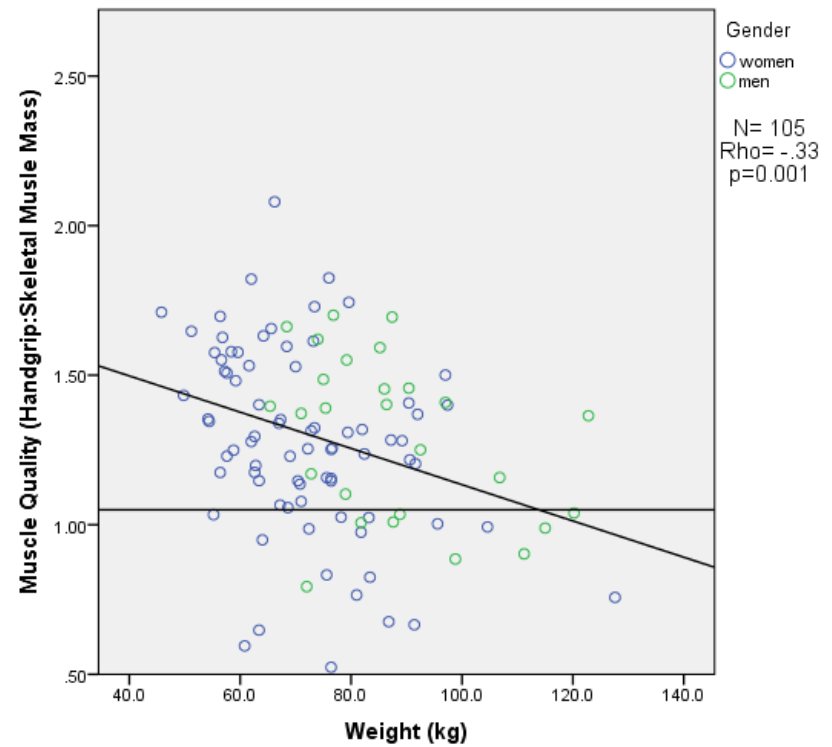
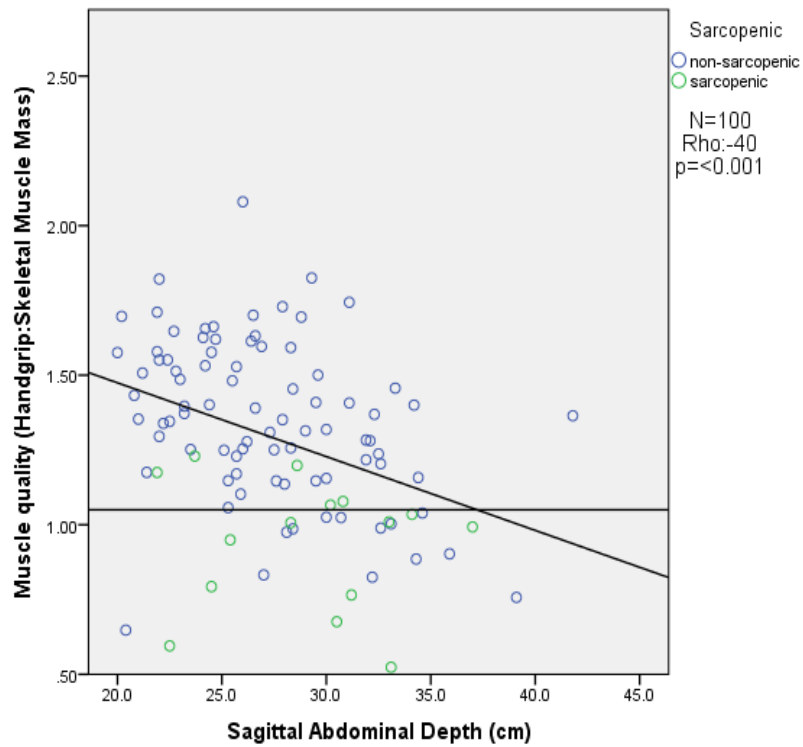


Figure 5.4 Association between muscle quality with SAD, and body weight. Left: association between muscle quality and sagittal abdominal diameter (cm). Right: Association between muscle quality and bodyweight (kg). A cut off is placed at the 25th percentile for muscle quality (1.06).

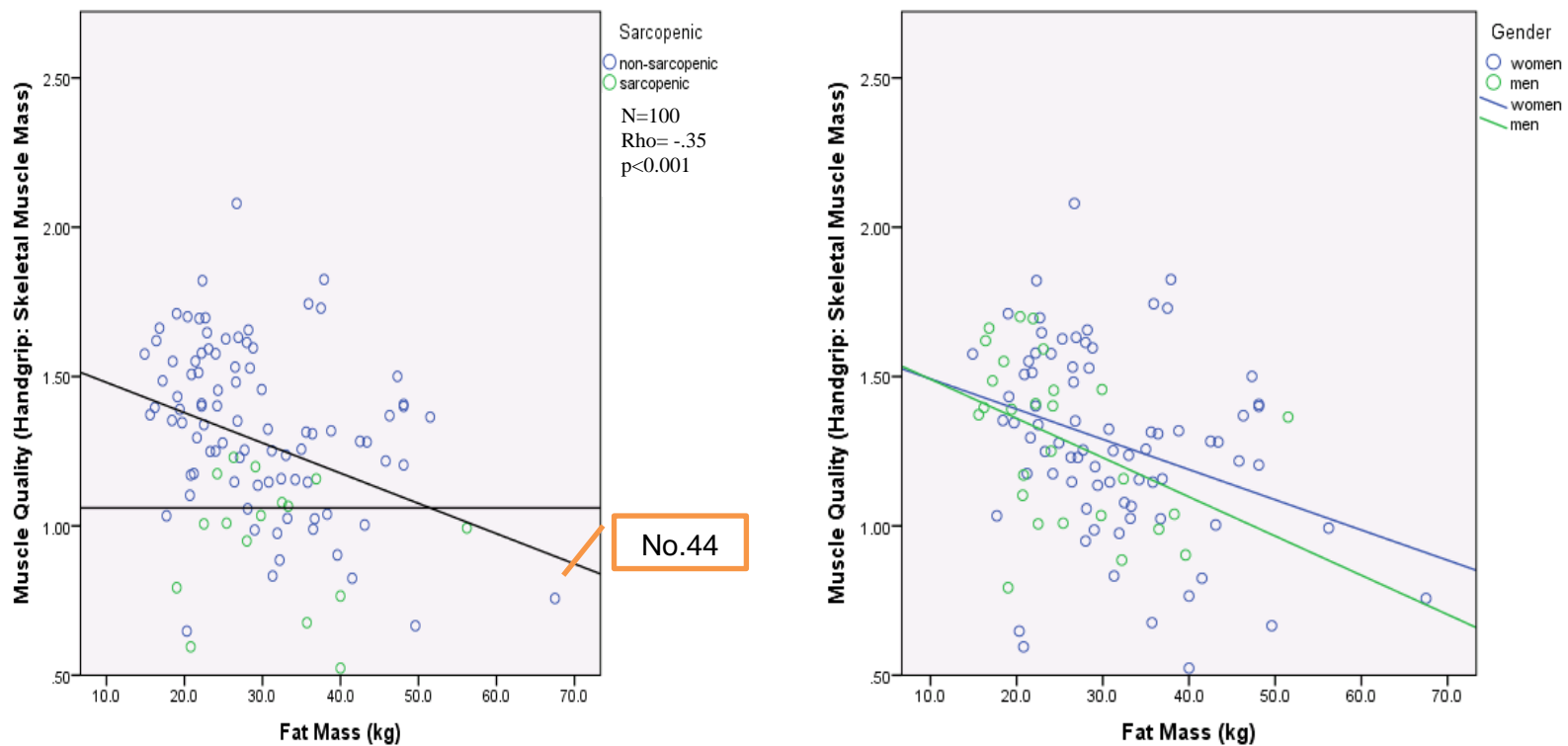


Figure 5.5 Association between muscle quality and fat mass. Left: a cut off is placed at the 25th percentile for muscle quality (1.06). The line of best fit applies to the overall cohort. Participant no.44 who was characterized by the highest fat mass and highest lean mass is highlighted in orange. Right: Correlation between muscle quality and FM in men ($n=29$, $Rho=-0.49$, $p=0.01$) and women ($n=78$, $Rho=-0.315$, $p=0.005$).

Chapter 6. Results: A complex exercise and high-protein intervention to augment body composition and function in older age. A randomised controlled trial.

Due to a small number of individuals who took part in the RCT, the requirements for a parametric analysis were not met, therefore a non-parametric/ descriptive approach was followed. Results are thus presented using medians (IQR: 25th, 75th percentile) and boxplots. Statistical comparisons for the RCT were performed at baseline before the drop-outs (n=18 participants, n=9 in each group). Namely, statistical comparisons were performed a) at baseline between EX vs EXD, b) between those who completed the study (completers) vs their counterparts who dropped-out before completing the study (non-completers), and c) between baseline dietary intakes of the female participants of the current study vs the national UK averages for women of the 65+ age group (section 6.2).

In total, 18 participants (women, n=16; men, n=2) were allocated to two groups, control (EX: exercise only) and intervention (EXD: Exercise and Diet) after application of the exclusion criteria (*section 6.1*) (recruitment flow was presented in **Figure 5.1**). All participants were Caucasian Scottish community-dwellers. Nine participants were allocated to each group (EX: n=9; EXD: n=9). Seven dropped out (EX, n=3; EXD, n=4) after being allocated to a group. Two participants dropped out before commencing with the programme, one (n=1) from EX and one (n=1) from EXD. Details for drop-outs are presented in *section 6.3 Drop outs*. Finally, n=6 participants from the EX group and n=5 participants from the EXD group, completed the study.

At the end of week16 the median (IQR) change in bodyweight was 0.5 (0.0, 1.0) kg in EX and -5.0 (-6.8, -5.0) kg in EXD. Skeletal muscle mass (SMM) increased by 0.5 (0.3, 0.7) kg in EX and by 0.1 (-0.4, 0.7) kg in EXD. Change in body fat was 0.0 (-0.4, 0.7) kg in EX and -4.7 (-4.8, -4.2)

kg in EXD. All body composition changes are presented in *section 6.4*. Median (IQR) changes in strength and function were: handgrip [EX: 1.5 (0.5, 1.5) kg; EXD: 1.0 (0.5, 2.0) kg], gait speed [EX: 0.4 (0.1, 0.5) m s⁻¹; EXD: 0.1 (-0.1, 0.3) m s⁻¹], timed up-and-go test [EX: -1.6 (-3.2, -1.0) s; EXD: -1.2 (-1.8, -1.0) s], SPPB [EX: 0.1 (0.0, 2.0); EXD: 1.0 (1.0, 1.0)], repeated chair stands [EX: -4.3 (-6.3, -2.3) s; EXD: -2.4 (-2.7, -2.2) s], 1-arm forward reach [EX: 7.6 (0.1, 9.1) cm; EXD: 1.3 (-5.1, 6.4) cm] (*section 6.5*). The most noticeable change in quality of life was in perceived overall health compared to previous year, where the median (IQR) score increased in both groups by 25 (0, 25) (*section 6.6*). Serum 25(OH)D concentrations increased numerically in both groups, in EX by 15 (-1, 31) nmol L⁻¹ and in EXD by 19 (9, 27) nmol L⁻¹ (*section 6.9*). Overall median (IQR) attendance to the exercise classes for those who completed the 16-week programme was 73 (67, 81) % (*section 6.10*). Adherence to diet and protein drink for the EXD group was 80 (70, 87) % and 92 (79, 95) %, respectively (*section 6.10*). Overall, changes in body composition were more pronounced in the EXD group, particularly in body weight and body fat, whereas both groups experienced positive changes in physical function and serum 25(OH)D concentrations at the end of 16-week research trial.

6.1 Exclusions

In total, 30 individuals met the inclusion criteria for body composition (**Figure 5.1**), but three (n=3) volunteers decided not to participate, due to difficulties in commuting or because they would only take part as a group with their friends/ spouses (**Table 6.1**). Of the remaining 27, seven (n=7) were excluded for health reasons (**Table 6.1**). One female participant was underweight (n=1), and although her %BF (41.5%) and SMI (5.02 kg m⁻²) were within the cut-off limits, she was excluded in order to prevent potential weight loss, especially if allocated in the diet group. Finally, one individual was excluded based on the cognitive assessment test.

Table 6.1 Exclusions from intervention study with reasons

Reasons	Details
Decided not to participate (n=3)	<ul style="list-style-type: none"> • Not residing close to university premises and unable to commute (n=1) • Friends/spouses not eligible to participate, thus the eligible participants decided not to participate on their own (n=2)
Health issues (n=7)	<ul style="list-style-type: none"> • Receiving corticosteroids, arthritis in several joints, gout, glaucoma and occasionally uncontrollable pain (n=1) • Receiving corticosteroids, abnormal blood tests indicating high inflammation (n=1) • Heart problems (n=2) • Severe osteoporosis (with recent fragility fractures) (n=1) • Double hernia, scheduled for operation within two months (n=1) • Recent health incident, suspected mini-stroke but still under investigation (n=1)
Other (n=2)	<ul style="list-style-type: none"> • Failed cognitive test (n=1) • Underweight, BMI=17.9 kg m⁻² (n=1)

6.2 Baseline characteristics of all participants in the RCT

Baseline characteristics are presented in **Table 6.2**. In EX, six out of the nine participants reported suffering from health conditions (hypertension: n=4; arthritis: n=3; fasting hyperglycemia: n=2, osteopenia: n=1, irritable bowel syndrome (IBS): n=1, depression: n=1, Barrett's esophagus: n=1), whereas three participants reported none. In EXD one out of nine participants did not report any conditions. Arthritis was reported by n=3, hypertension by n=3, high cholesterol by n=1, fasting hyperglycemia n=1, osteopenia n=1, uncontrolled coughing n=1, stroke survivor n=1). Apart from sarcopenic obesity, out of the 18 participants in total, seven reported to suffer from more than one condition.

No significant differences were observed at baseline for any of the body composition or physical function parameters, serum 25(OH)D concentrations (**Table 6.2**), or quality of life (**Table 6.3**). Median (IQR) age was 74 (71, 77) yr and 73 (68, 76) yr in EX and EXD, respectively. At baseline, both groups scored 70 or higher in all subsections of the quality of life questionnaire, with the exceptions being '*Energy & Fatigue*', EX: 45 (38, 65), '*change in health since previous year*', EX: 50 (50, 56); EXD: 50 (50, 75) and '*general health*' EXD: 65 (55, 88), but no significant differences were detected at baseline between groups (**Table 6.3**).

Baseline dietary intakes before the drop-outs (n=18) are presented in **Table 6.4**. The EX group reported a daily energy intake (EI) of 1554 (1489, 1745) kcal, and the EXD group an EI of 1627 (1469, 1749) kcal. Daily protein intakes relative to bodyweight in EX vs EXD at baseline were 0.9 (0.8, 1.1) g kg bw⁻¹ vs 0.8 (0.7, 1.2) g kg bw⁻¹, respectively. Protein distribution in the three main meals (breakfast, lunch, dinner) for the overall group (n=18) was 10 (7, 16) g, 19 (13, 23) g and 30 (21, 34) g. The respective values for EX vs EXD at baseline were 10 (9, 15) g vs 10 (6, 12) g, 22 (16, 23) g vs 16 (14, 21) g and 28 (17, 35) g vs 30 (23, 32) g for breakfast, lunch and dinner (**Figure 6.1**). No significant differences were detected between the two groups at baseline. The current cohort of women at baseline (n=16) reported significantly higher energy intakes than the national average, 1605 (1526, 1695) kcal vs 1483 kcal, respectively (p=0.039), but significantly lower % contribution protein to energy intake, 15.1 (13.8, 16.7) % vs 17.5% (p=0.008). No other differences were noted in the remaining dietary intake values.

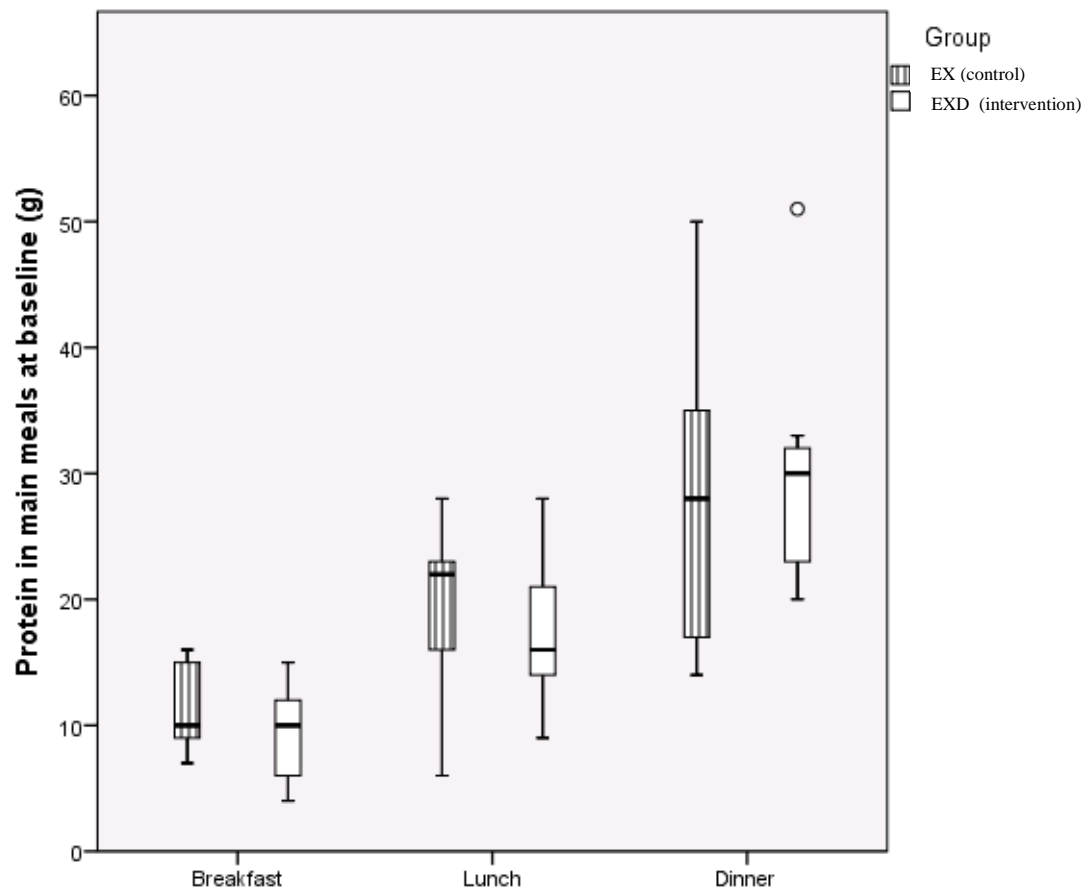


Figure 6.1 Boxplots with protein intakes in the main meals at baseline. Between groups differences at baseline for protein intake in breakfast ($p=0.286$), lunch ($p=0.452$) and dinner ($p=0.791$) were non significant. EX: $n=9$, EXD: $n=9$.

Table 6.2 Baseline body composition, function and Vitamin D 25(OH) measurements, overall and between group comparisons.

	Overall (n=18)		EX (n=9) ¹		EXD (n=9) ¹		<i>p</i> (sig.) value
	Median	(IQR)	Median	(IQR)	Median	(IQR)	
Age	74	(69, 76)	74	(71, 77)	73	(68, 76)	0.450
Weight (kg)	68.3	(57.4, 76.1)	66.2	(56.4, 75.0)	70.4	(58.4, 82.4)	0.453
Height (kg)	160.9	(152.9, 164.8)	157.4	(152.8, 164.0)	162.5	(153.0, 166.5)	0.453
BMI (kg m ⁻²)	26.8	(24.0, 28.9)	26.9	(23.3, 28.7)	26.7	(25.0, 29.0)	0.566
%BF	44.6	(40.5, 47.2)	44.7	(40.3, 48.7)	44.5	(41.8, 47.8)	0.895
FM (kg)	28.7	(25.4, 33.8)	26.7	(23.6, 35.1)	29.5	(26.5, 34.4)	0.354
SMM (kg)	15.4	(14.4, 17.7)	15.3	(14.3, 16.7)	16.3	(14.2, 18.7)	0.691
SMI (km m ⁻²)	6.31	(5.95, 6.65)	6.20	(5.92, 6.58)	6.42	(5.95, 6.76)	0.724
SAD (cm)	27.0	(24.0, 31.4)	27.9	(22.3, 31.9)	25.7	(24.15, 31.8)	0.691
Handgrip (kg)	22.8	(18.3, 27.3)	23.0	(17.3, 27.8)	22.5	(19.5, 27.5)	0.627
Muscle Quality	1.36	(1.07, 1.67)	1.20	(1.04, 1.71)	1.48	(1.09, 1.64)	0.965
SBP (mmHg)	138	(127, 147)	134	(124, 140)	146	(130, 153)	0.200
DBP (mmHg)	69	(75, 82)	74	(73, 83)	76	(66, 82)	0.507
HR (bpm)	64	(69, 77)	70	(65, 77)	68	(62, 78)	0.689
SPPB	11	(10, 12)	11	(11, 12)	11	(8, 12)	0.463
GS (m s ⁻¹)	1.1	(1.0, 1.2)	1.0	(0.9, 1.2)	1.1	(1.0, 1.2)	0.289
RCS (s)	12.1	(9.3, 14.8)	12.0	(8.5, 13.5)	12.3	(9.5, 16.8)	0.402

1-Arm Reach (cm)	27.6	(23.2, 32.4)	25.7	(22.9, 32.6)	28.1	(25.1, 33.6)	0.566
TUG (s)	6.7	(5.5, 7.2)	6.7	(5.5, 7.3)	6.7	(5.4, 7.6)	1.000
25(OH)D (nmol L ⁻¹)	57	(48, 67)	49	(43, 61)	60	(49, 83)	0.223

%BF, percent body fat; ¹ men: n=1, women: n=8; BMI, body mass index; DBP, diastolic blood pressure; GS, gait speed; FM, fat mass; HR, heart rate; LM, lean mass; Muscle Quality= Handgrip (kg): SMM (kg); RCS, repeated chair stands; SAD, sagittal abdominal diameter; SBP, systolic blood pressure; SMI, skeletal muscle index; SMM, skeletal muscle mass; SPPB, short physical performance battery test; TUG, timed up and go

Table 6.3 Health Related Quality of Life (HRQoL) at baseline, overall, and between group comparisons.

	overall (n=18)		EX (n=9) ¹		EXD (n=9) ¹		<i>p</i> (sig.) value
	median	IQR	Median	IQR	Median	IQR	
Physical Functioning	78	(69, 86)	70	(60, 85)	80	(70, 90)	0.265
Role limitations due to physical health	88	(44, 100)	75	(38, 88)	100	(50, 100)	0.118
Role limitations due to emotional problems	100	(92, 100)	100	(33, 100)	100	(100, 100)	0.249
Energy & fatigue	55	(44, 81)	45	(38, 65)	80	(55, 85)	0.074
Emotional well-being	78	(67, 92)	76	(62, 80)	88	(74, 94)	0.051
Social Functioning	88	(63, 100)	75	(50, 100)	100	(75, 100)	0.164
Pain	79	(64, 90)	78	(50, 95)	90	(68, 90)	0.419
General health	68	(54, 86)	70	(48, 85)	65	(55, 88)	0.894
Change in health from previous year	50	(50, 56)	50	(50, 50)	50	(50, 75)	0.370

Scores can range from 0 to 100, with higher scores indicating a higher quality of life. ¹ men: n=1, women: n=8

Table 6.4 Overall baseline dietary intakes and differences between groups before the drop-outs.

	Overall (n=18)		EX (n=9) ¹		EXD (n=9) ¹		p (sig. value)
	Median	IQR	Median	IQR	Median	IQR	
Daily Energy Intake (kcal)	1617	(1483, 1729)	1554	(1489, 1745)	1627	(1469, 1749)	.825
Daily Energy intake relative to bodyweight (kcal · kg bw ⁻¹)	24.6	(21.1, 26.2)	24.1	(21.4, 27.2)	24.1	(21.9, 26.8)	.757
Daily Protein Intake (g)	61	(53, 70)	58	(51, 71)	66	(55, 70)	0.453
Contribution protein to EI (%)	15	(14, 17)	15	(14, 18)	15	(13, 18)	0.825
Daily Protein Intake Relative to bodyweight (g · kg bw ⁻¹)	0.9	(0.8, 1.1)	0.9	(0.8, 1.1)	0.8	(0.7, 1.2)	0.691
Daily CHO Intake (g)	184	(124, 210)	181	(163, 201)	198	(130, 217)	0.691
Contribution CHO to EI (%)	45	(42, 48)	45	(43, 48)	47	(34, 51)	0.895
Daily Fat Intake (g)	65	(54, 78)	66	(56, 78)	63	(48, 80)	0.627
Contribution Fat to EI (%)	36	(32, 41)	37	(34, 43)	34	(28, 39)	0.145
Daily Sat. Fat Intake (g)	23	(18, 30)	24	(19, 31)	21	(16, 28)	0.423
Contribution Sat. Fat to EI (%)	14	(11, 16)	14	(11, 17)	14	(12, 16)	0.200
Free sugar Intake (g)	28	(17, 50)	28	(20, 49)	30	(15, 51)	0.743
Contribution free sugar to EI (%)	8	(4, 12)	8	(6, 12)	8	(4, 12)	0.541
Dietary Fibre (g)	17	(15, 20)	17	(14, 20)	17	(15, 20)	0.730
Vitamin D intake (µg)	2.3	(1.1, 4.3)	2.9	(1.4, 3.9)	2.3	(1.5, 4.4)	0.888
Calcium intake (mg)	746	(665, 836)	723	(665, 795)	752	(674, 907)	0.541

¹ men: n=1, women: n=8; Bw, bodyweight; CHO, carbohydrates; EI, energy intake.

6.3 Drop outs

Seven people (n=7) dropped out from the programme after they had been allocated to a group. The comparison at baseline between the participants who completed the study (n=11) against those who were lost to follow-up ('non-completers'), revealed that the non-completers had significantly higher SMM than the completers, namely 16.3 (15.4, 28.5) kg vs 14.5 (14.0, 17.1) kg ($p=0.042$) (**Table 6.5**). The only two men who were allocated to a study group were both non-completers, as they dropped out. Although non-completers had a significantly greater muscle mass, they had a significantly lower gait speed [1.0 ($0.8, 1.1$) m s^{-1}] than their counterparts who completed the study [1.1 ($1.0, 1.3$) m s^{-1}] ($p=0.020$). No other differences were found in any of the anthropometry and function indices (weight, height, BMI, %BF, FM, handgrip, muscle quality, SPPB, repeated chair stands, single-arm forward reach and timed up-and-go test) (**Table 6.5**). No significant differences were noted in quality of life domains, and dietary intakes between the two groups, with the exception of free sugar intake [non-completers: 48 (36, 55) g vs completers: 21 (15, 28) g in ($p=0.019$)] and free sugar relative contribution to energy intake [non-completers: 9 (8, 14) % vs completers: 6 (4, 8) % ($p=0.014$)].

In EX, three participants were lost to follow-up. One person dropped out after completing all the assessment tests and being allocated to a group but before commencing with the exercise classes due to lack of time. Two participants dropped out after commencing the exercise programme. One woman dropped out at week-7; however, she last attended the exercise classes in week-4 and then went on a two-week holiday. Upon her return she informed the researcher about a discomfort at the neck area, which was reported to be a trapped nerve (according to the general practitioner (GP) who performed an examination) and thus, after a discussion with the researcher of the current study it was decided that she should stop the exercise classes until full recovery. The second

participant was informed in week-4 that they were suffering from heart disease after receiving a medical health check and had to undergo further medical examinations.

Table 6.5 Differences in body composition and physical function at baseline between the participants who completed the study (completers) and those who dropped out before completing the study (non-completers).

	completers (n=11)		non-completers (n=7) ¹		p (sig.) value
	median	IQR	median	IQR	
Age	73	(68, 74)	76	(73, 83)	0.075
Weight (kg)	66.2	(56.4, 76)	70.4	(62.8, 87.6)	0.441
Height (cm)	157.4	(152.9, 164.4)	162.4	(152.7, 174.6)	0.390
BMI(kg m ⁻²)	25.2	(23.8, 29.9)	26.9	(25.6, 27.5)	0.526
%BF	44.7	(40.6, 51.1)	43.7	(33.6, 45.8)	0.342
FM (kg)	26.7	(24.2, 37.9)	29.1	(26.6, 30.8)	0.751
SMM (kg)	14.5	(14.0, 17.1)	16.3	(15.4, 28.5)	0.042
SMI (kg m ⁻²)	6.05	(5.84, 6.54)	6.61	(6.20, 9.17)	0.051
Handgrip (kg)	23.0	(17.0, 26.5)	22.0	(18.5, 29.5)	0.683
Muscle Quality	1.63	(1.17, 1.73)	1.15	(1.03, 1.48)	0.135
SPPB	11	(10, 12)	11	(9, 12)	0.814
GS (m s ⁻¹)	1.1	(1.0, 1.3)	1.0	(0.8, 1.1)	0.020
RCS (s)	12.1	(9, 14.3)	12	(9.4, 17.3)	0.930
1-Arm Reach (cm)	30.7	(23.04, 35.8)	27	(22.6, 28.2)	0.135
TUG (s)	6.7	(5.6, 7.5)	6.7	(5.4, 7.1)	0.964

¹ men: n=2, women: n=5; 8%BF, percent body fat; BMI, body mass index; GS, gait speed; FM, fat mass; LM, lean mass; RCS, repeated chair stands; SMI, skeletal muscle index; SMM, skeletal muscle mass; SPPB, short physical performance battery test; TUG, timed up and go

Four participants dropped out from the EXD group. One was admitted to hospital with a chest infection prior to commencing the exercise and diet regimen and decided to drop out before starting with the programme. Another participant had been suffering from flare-ups of coughing due to unknown cause before commencing with the programme, and decided to drop-out for the same reason on the first day of the programme. The third participant decided to drop out at week-3 after being home-bound for one week with symptoms of the seasonal flu. She reported that her peers and family members discouraged her from continuing with the programme as she was told that it is not something appropriate for her age. The fourth participant suffered a mini stroke at week-9 and dropped out.

The exercise programme was generally well tolerated and no injuries were noted. There was one incident of a fall which was due to inappropriate footwear rather than weakness or poor balance. Although the participant who experienced the fall was happy to continue with the exercises, they were asked by the researcher to refrain from exercises for the rest of the day, and were present at the subsequent class, with no evidence of injury or discomfort.

All results presented in the following sections refer to those participants who completed the programme, that is, 11 participants in total, six in the control (EX) and five in the intervention group (EXD). It was not possible to collect blood samples from one participant (EX group) at both time points (baseline and week-16), and from one participant at baseline from the EXD group.

6.4 Body composition

Body composition changes in all participants who completed the study (EX: n=6; EXD: n=5) are presented in **Table 6.6**. From baseline to week16, participants in EX experienced a median (IQR) gain in bodyweight of 0.5 (0.0, 1.0) kg, whereas the EXD group lost 5.0 (5.0, 6.8) kg of bodyweight (**Figure 6.2**). It is important to note that the difference of the medians for any given variable does not necessarily coincide with the median differences for the same time points. For example, median bodyweight at baseline and week16 in EXD was 72.6 kg and 69.1 kg, respectively (**Table 6.6**), but the median change in bodyweight in EXD for the same period was 5.0 kg (as presented in more detail in **Table 6.7**).

Changes in body weight were mainly accounted for by changes in fat mass and skeletal muscle mass. In terms of absolute fat mass, the median fat mass change in EXD group was -4.7 (-4.8, -4.2) kg, whereas EX group experienced a change of 0.0 (-0.4, 0.7) kg (**Figure 6.2**). The median change of SMM was positive in both groups [EX: 0.5 (0.3, 0.7) kg; EXD: 0.1 (-0.4, 0.7) kg] (**Figure 6.2**). The median change in the ratio of fat mass to skeletal muscle mass (FM: SMM) in week16 was -0.05 (-0.13, 0.00) in EX and -0.35 (-0.37, -0.25) in EXD.

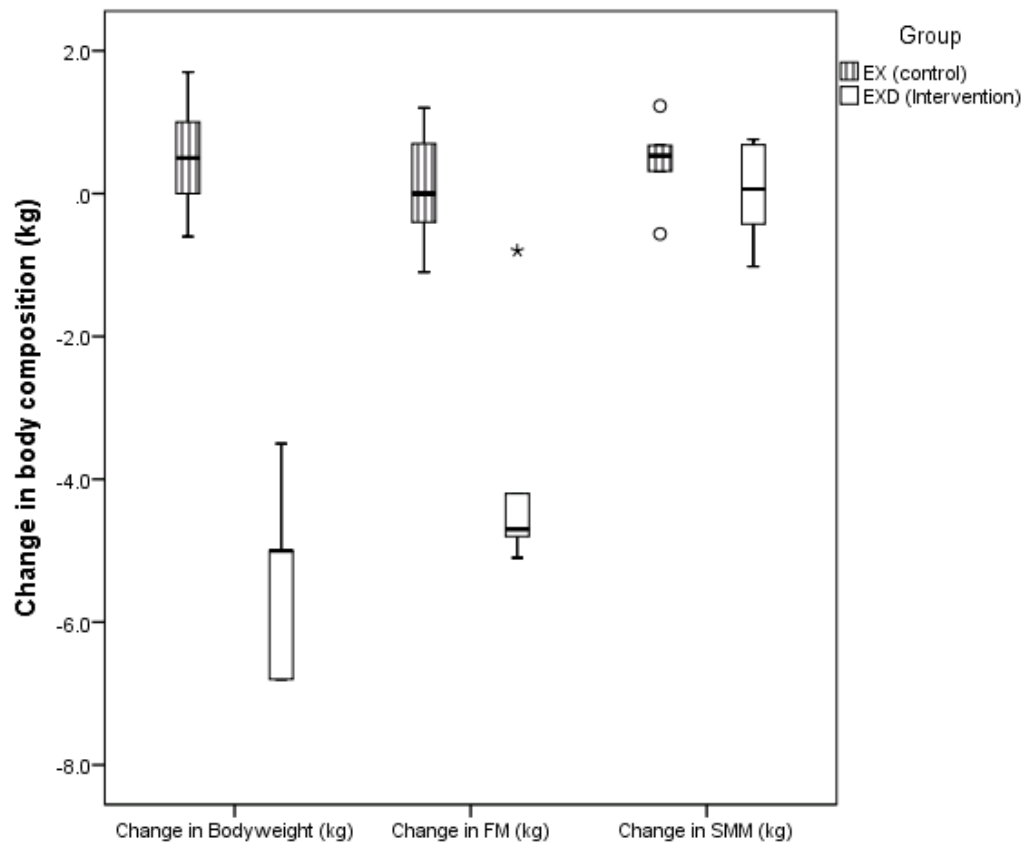


Figure 6.2 Boxplots with changes in bodyweight (kg), fat mass (kg) and skeletal muscle mass (kg) from baseline to week16 for the EX and EXD groups. EX: n=6; EXD: n=5.

Table 6.6 Body composition changes over the course of 16 weeks for the two groups of participants who completed the study.

		Baseline		Week 10		Week 16		Median (IQR) change baseline-week16
		median	IQR	median	IQR	median	IQR	
EX n=6	Weight (kg)	61.3	(55.1, 74.2)	62.4	(53.8, 73.9)	62.2	(54.7, 75.5)	0.5 (0.0, 1.0)
	BMI (kg m ⁻²)	23.9	(22.6, 30.6)	23.9	(22.8, 30.6)	24.1	(22.9, 31.4)	0.3 (0.1, 0.4)
	%BF	43.8	(40.3, 51.4)	43.7	(39.1, 51.6)	43.7	(39.1, 51.8)	-0.2 (-1.4, 0.5)
	FM (kg)	25.5	(22.9, 38.2)	25.0	(22.9, 38.1)	25.3	(23.1, 39.1)	-0.1 (-0.4, 0.7)
	SMM (kg)	14.9	(14.1, 15.8)	15.4	(13.8, 16.2)	15.7	(14.3, 16.4)	0.5 (0.3, 0.7)
	SMI (kg m ⁻²)	6.09	(5.82, 6.50)	6.20	(5.94, 6.60)	6.31	(6.16, 6.50)	0.22 (0.18, 0.29)
	SAD (cm)	22.7	(21.1, 27.0)	22.0	(20.2, 25.6)	22.4	(20.9, 25.1)	-1.3 (-1.7, -0.3)
	FM:SMM	1.66	(1.54, 2.63)	1.65	(1.41, 2.65)	1.64	(1.47, 2.59)	-0.05 (-0.13, 0.00)
EXD n=5	Weight (kg)	72.6	(57.2, 90.3)	70.6	(51.8, 86.6)	69.1	(50.4, 85.3)	-5.0 (-6.8, -5.0)
	BMI (kg m ⁻²)	26.9	(24.6, 32.8)	26.2	(22.4, 31.5)	25.7	(21.8, 31.0)	-1.9 (-2.7, -1.8)
	%BF	45.7	(42.6, 51.8)	44.0	(42.2, 49.7)	43.5	(41.4, 49.0)	-2.4 (-3.3, -2.2)
	FM (kg)	29.5	(25.8, 47.1)	29.8	(22.4, 43.3)	28.7	(21.4, 42.1)	-4.7 (-4.8, -4.2)
	SMM (kg)	14.5	(13.8, 18.7)	14.8	(13.7, 19.0)	15.2	(13.7, 18.6)	0.1 (-0.4, 0.7)
	SMI (kg m ⁻²)	6.05	(5.67, 6.76)	5.95	(5.71, 6.87)	5.94	(5.83, 6.73)	0.05 (-0.11, 0.26)
	SAD (cm)	25.7	(23.9, 33.2)	26.0	(22.2, 32.5)	24.4	(20.7, 31.3)	-2.0 (-3.1, -1.8)
	FM:SMM	1.90	(1.72, 2.77)	1.72	(1.63, 2.44)	1.66	(1.57, 2.37)	-0.35 (-0.37, -0.25)

%BF, percent body fat; BMI, body mass index; FM, fat mass; FM:SMM, fat mass to skeletal muscle mass ratio; LM, lean mass; SAD, sagittal abdominal diameter; SMI, skeletal muscle index; SMM, skeletal muscle; mass.

Table 6.7 Median bodyweight at baseline, week16 and median bodyweight change between the two time points.

Group	Participant No.	Bodyweight (kg) baseline	Bodyweight (kg) week16	Weight change (kg)
EX	2	56.4	57.4	1.0
	43	66.2	67.0	0.8
	53	73.5	75.2	1.7
	91	76.4	76.4	0.0
	102	56.4	55.8	-0.6
	105	51.2	51.4	0.2
	Median	61.3	62.2	0.5
EXD	5	104.6	99.6	-5.0
	20	57.6	50.8	-6.8
	49	56.8	50.0	-6.8
	62	76.0	71.0	-5.0
	107	72.6	69.1	-3.5
	median	72.6	69.1	-5.0

6.5 Strength & Physical performance

All median (IQR) scores from the physical assessment tests performed at baseline, week10 and week16 along with median changes from baseline to week16 are presented in **Table 6.8**. A numerical improvement was noted in both groups from baseline to follow-up at week16 in all tests (handgrip, SPPB, gait speed, repeated chair stands (RCS), 1-arm reach, and timed up-and-go (TUG)), and muscle quality. The most noticeable change was that in time to complete five RCSs in both groups [EX: -4.3 (6.3,-2.3) s; EXD: -2.4 (-2.7,-2.2) s], TUG [EX: -1.6 (-3.2,-1.0) s; EXD: -1.2 (-1.8,-1.0) s] (**Figure 6.3**), and 1-Arm reach distance in EX: 7.6 (0.1, 9.1) cm.

Table 6.8 Physical function changes over the course of 16 weeks for the two groups of participants who completed the study.

		Baseline		Week 10		Week 16		Median (IQR) change baseline- week16
		median	IQR	median	IQR	median	IQR	
EX	HG (kg)	24.5	(20.0, 30.8)	24.0	(21.3, 31.8)	26.0	(20.8, 31.8)	1.5 (0.5, 1.5)
(n=6)	Muscle Quality	1.67	(1.01, 1.82)	1.73	(1.48, 1.88)	1.66	(1.43, 1.94)	0.10 (-0.04, 0.05)
	SPPB	12	(10, 12)	12	(12, 12)	12	(12, 12)	0 (0, 2)
	GS (m s ⁻¹)	1.1	(1.0, 1.3)	1.4	(1.3, 1.6)	1.4	(1.4, 1.7)	0.4 (0.1, 0.5)
	RCS (s)	10.57	(7.87, 15.40)	7.56	(6.18, 8.08)	6.84	(5.57, 8.07)	-4.3 (-6.3,-2.3)
	1-Arm Reach (cm)	28.3	(23.3, 33.1)	32.9	(29.9, 35.9)	34.1	(32.3, 35.8)	7.6 (0.1,9.1)
	TUG (s)	6.23	(5.30, 7.85)	4.85	(4.42, 5.17)	4.36	(4.08, 4.73)	-1.6 (-3.2,-1.0)
EXD	HG (kg)	22.5	(18.0, 27.3)	23.5	(20.5, 28.8)	24.5	(19.0, 28.0)	1.0 (0.5, 2.0)
(n=5)	Muscle Quality	1.53	(1.11, 1.73)	1.66	(1.25, 1.80)	1.68	(1.27, 1.76)	0.06 (0.04, 0.14)
	SPPB	11	(9, 12)	12	(11, 12)	12	(12, 12)	1 (1,1)
	GS (m s ⁻¹)	1.1	(1.1, 1.3)	1.2	(1.0, 1.4)	1.3	(1.1, 1.6)	0.1 (-0.1, 0.3)
	RCS (s)	12.27	(10.80, 15.10)	9.76	(8.02, 15.48)	9.80	(7.42, 11.40)	-2.4 (-2.7,-2.2)
	1-Arm Reach (cm)	30.7	(25.2, 37.8)	32.7	(28.5, 34.2)	31.9	(28.1, 35.6)	1.3 (-5.1,6.4)
	TUG (s)	6.73	(5.61, 7.64)	5.67	(4.31, 6.98)	4.91	(4.56, 6.80)	-1.2 (-1.8,-1.0)

GS, gait speed; RCS, repeated chair stands; SPPB, short physical performance battery test; TUG, timed up and go

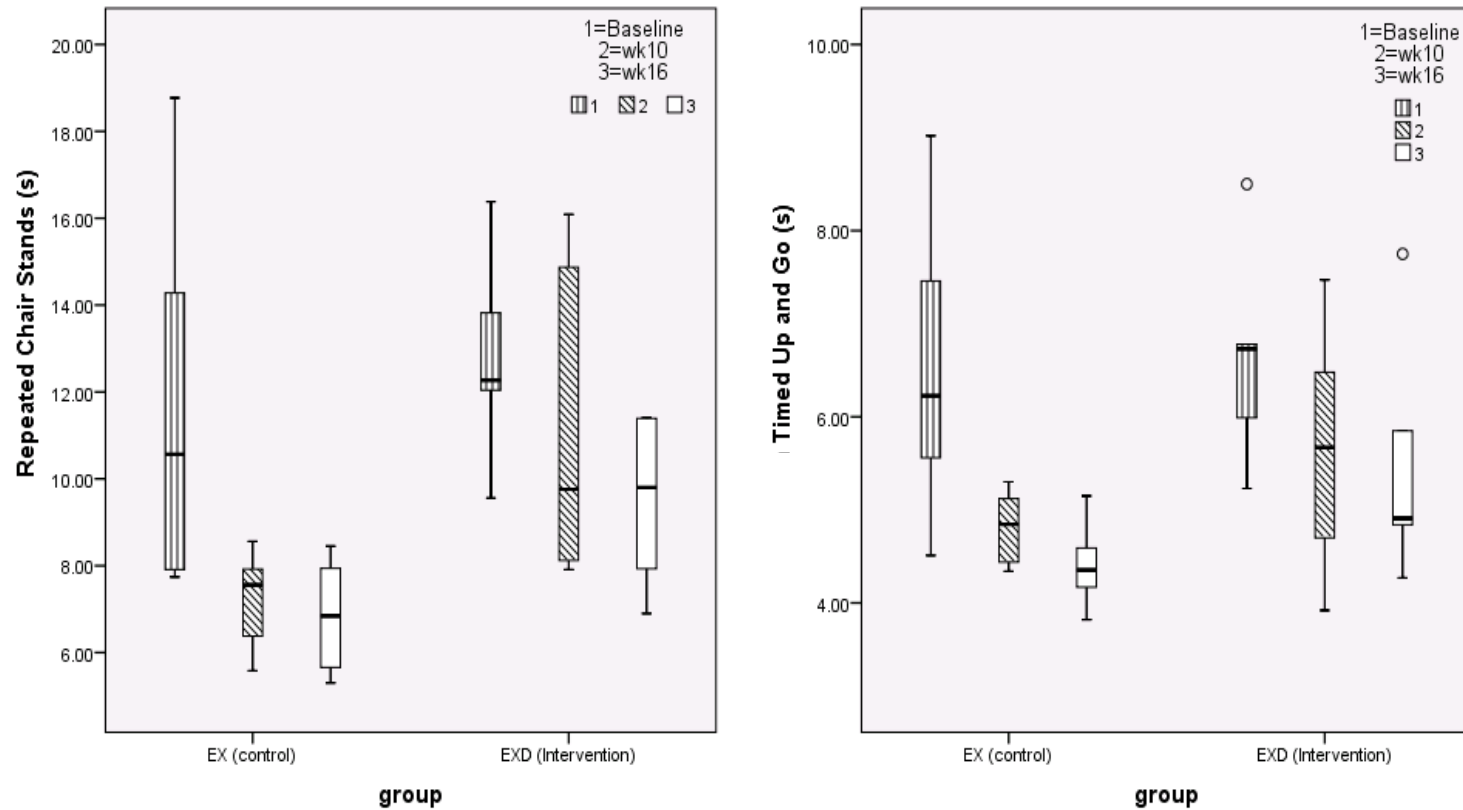


Figure 6.3 Boxplots with time to complete Repeated Chair Stands and a Timed Up and Go test, at baseline, week10 and week16. Left: Boxplots with time (s) to complete 5 repeated chair stands (RCS); Right: Boxplots with time (s) to complete a timed get up-and-go (TUG) test; $n=6$ in EX and $n=5$ in EXD.

6.6 Health Related Quality of Life (HRQoL)

Median (IQR) baseline and week16 values, as well as the median changes (IQR) in domains of health related quality of life are presented in detail in **Table 6.9**. Higher values for each domain indicate better quality of life. In EX, the median change from baseline to week16, was positive for all domains with the exception of perceived 'Pain' [median (IQR) change : 0 (-13, 13)]. A median change of 0 (0, 33) was also noted for the domain 'Role limitations due to emotional problems', however, that domain had scored the maximum points at baseline (100), hence the zero median change. Similarly, in EXD three domains ('Role limitations due to physical health', 'Role limitations due to emotional problems' and 'Social Functioning') scored a median of 100 points at baseline, and thus the median change from baseline to week16 was zero. In EXD, three negative changes were noted in 'Energy/ fatigue' [-5 (-5, 5)], 'Emotional well-being' [-8 (-12, 0)], and 'Pain' [-10 (-13, 0)]. The median increase in perceived 'Change in health in comparison to one year ago' was the same in both groups 25 (0, 25).

Table 6.9 Changes in Perceived Health Related Quality of Life (HRQoL) in the EX and EXD groups from baseline to week16.

	EX (n=6)					EXD (n=5)				
	Baseline		Week 16		Median (IQR) change baseline- week16	Baseline		Week 16		Median (IQR) change baseline- week16
	median	IQR	median	IQR		median	IQR	median	IQR	
Physical Functioning	70	(63, 90)	85	(74, 91)	10 (5, 15)	80	(70, 88)	80	(75, 98)	5 (0, 10)
Role limitations due to physical health	63	(44, 81)	100	(38, 100)	13 (0, 25)	100	(50, 100)	100	(88, 100)	0 (0, 0)
Role limitations due to emotional problems	100	(50, 100)	100	(58, 100)	0 (0, 33)	100	(67, 100)	100	(83, 100)	0 (0, 0)
Energy/ fatigue	48	(35, 63)	65	(46, 76)	15 (0, 20)	80	(40, 83)	75	(60, 85)	-5 (-5, 5)
Emotional well-being	74	(52, 86)	84	(70, 88)	4 (4, 24)	88	(74, 94)	76	(74, 86)	-8 (-12, 0)
Social Functioning	81	(47, 100)	100	(66, 100)	6 (0, 25)	100	(75, 100)	100	(100, 100)	0 (0, 13)
Pain	78	(53, 93)	73	(59, 93)	0 (-13, 13)	80	(68, 95)	68	(63, 90)	-10 (-13, 0)
General health	68	(44, 76)	73	(59, 93)	8 (5, 25)	65	(55, 88)	75	(68, 93)	10 (5, 20)
Change from previous year	50	(44, 50)	63	(50, 81)	25 (0, 25)	50	(38, 75)	75	(63, 100)	25 (0, 25)

Scores for each domain can range from 0 to 100, with higher scores indicating better quality of life.

6.7 Dietary intakes

Median (IQR) energy intake at baseline and week-16 in EX ($n=6$) was 1546 (1502, 1704) kcal and 1531 (1343, 1601) kcal, respectively. In EXD ($n=5$) baseline energy intake was 1627 (1527, 1749) kcal, final was 1294 (1156, 1410) kcal, and the median change between the two time periods was -473 (-492, -333) kcal (**Table 6.10**). Absolute protein intake in EX was 57 (54, 60) g at baseline and 57 (51, 64) g at week16, whereas in EXD, 66 (61, 69) g at baseline and 97 (84, 102) at week16 (**Figure 6.4**). The median increase in absolute protein intakes in EXD was 35 (27, 36) g. The median protein intake relative to bodyweight remained the same from baseline to week16 in EX [0.9 ($0.8, 1.1$) g kg bw^{-1}]. In EXD it increased by 0.4 ($0.4, 0.6$) g kg bw^{-1} to reach 1.4 (1.1 - 1.7 g) at week-16. In general, dietary intakes remained relatively stable in EX. In EXD carbohydrate (including free sugars), fat and saturated fat intakes, and their % contribution to total energy intake were numerically reduced. Vitamin D intakes (including supplementation) increased in both groups, in EX by 10.3 ($2.9, 10.6$) μg and in EXD by 9.0 ($7.1, 10.0$) μg . Calcium intakes changed by -40 ($-97, 113$) mg in EX and by 265 ($133, 456$) mg in EXD. All dietary intake median values from baseline and week16 (and median changes for the same period) are presented in **Table 6.10**.

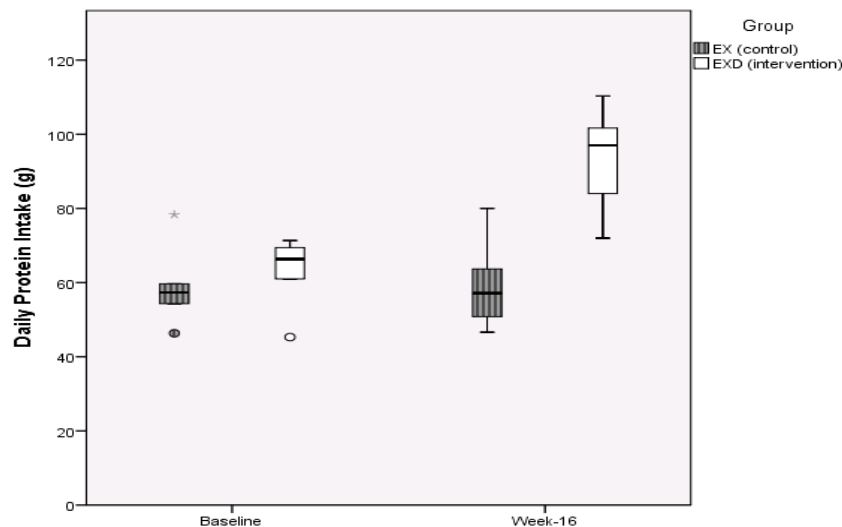


Figure 6.4 Boxplots with median (IQR) daily protein intake (g) at baseline and week-16 in EX (control; $n=6$) and EXD (intervention; $n=5$) groups.

Table 6.10 Baseline and follow-up dietary intakes in EX (control) and EXD (intervention) for those who completed the study.

	EX (n=6)						EXD (n=5)					
	Baseline		Week16		Median change (IQR) baseline to week16		Baseline		Week16		Median change (IQR) baseline to Week16	
	Median	IQR	Median	IQR			Median	IQR	Median	IQR		
Daily Energy Intake (kcal)	1546	(1502, 1704)	1531	(1343, 1601)	-7 (-199, 27)		1627	(1527, 1749)	1294	(1156, 1410)	-473 (-492, -333)	
Daily Energy Intake relative to bodyweight (kcal·kg bw ⁻¹)	26.4	(21.7, 28.1)	24.1	(19.5, 28.4)	-0.2 (-4.5, 0.6)		22.4	(19.1, 27.6)	18.7	(14.4, 26.9)	-3.9 (-5.4, -3.7)	
Daily Protein Intake (g)	57	(54, 60)	57	(51, 64)	5 (-10, 8)		66	(61, 69)	97	(84, 102)	35 (27, 36)	
Contribution Protein to EI (%)	14	(13, 16)	17	(13, 19)	2 (-3, 5)		15	(13, 18)	29	(26, 34)	14 (12, 18)	
Daily Protein Intake Relative to bodyweight (g·kg bw ⁻¹)	0.9	(0.8, 1.1)	0.9	(0.8, 1.1)	0.1 (-0.2, 0.1)		0.8	(0.6, 1.2)	1.4	(1.1, 1.7)	0.4 (0.4, 0.6)	

Daily CHO Intake (g)	173	(163, 197)	175	(144, 190)	9 (-51, 13)	170	(130, 210)	131	(120, 172)	-25 (-46, -2)
Contribution CHO to EI (%)	46	(42, 48)	46	(43, 48)	1 (-4, 3)	45	(39, 53)	45	(32, 49)	-4 (-7, -2)
Daily Fat Intake (g)	65	(59, 81)	61	(54, 72)	-3 (-9, 3)	55	(46, 80)	36	(20, 42)	-27 (-34, -19)
Contribution Fat to EI (%)	38	(32, 46)	37	(35, 40)	2 (-5, 4)	32	(25, 44)	25	(15, 27)	-10 (-13, -8)
Daily Sat. Fat Intake (g)	25	(21, 32)	21	(20, 36)	-1 (-5, 6)	17	(15, 22)	14	(10, 16)	-5 (-6, -4)
Contribution Sat.Fat to EI (%)	15	(11, 18)	14	(12, 21)	1 (-2, 5)	10	(8, 13)	9	(7, 11)	-1 (-2, 1)
Daily Free Sugar Intake (g)	26	(17, 46)	20	(19, 50)	2 (-5, 15)	15	(13, 25)	6	(4, 22)	-8 (-16, 3)
Contribution Free Sugar to EI (%)	7	(4, 11)	6	(5, 12)	1 (-1, 4)	4	(3, 6)	2	(1, 7)	-2 (-4, 2)
Daily Dietary Fibre Intake (g)	18	(15, 20)	16	(8, 18)	-2 (-6, 0)	18	(13, 20)	16	(13, 18)	-2 (-4, -1)
Vitamin D intake (µg)	2.2	(0.7, 4.8)	10.9	(10.5, 14.5)	10.3 (2.9, 10.6)	4.4	(2.6, 7.5)	13.1	(11.9, 14.8)	9.0 (7.1, 10.0)
Calcium intake (mg)	708	(584, 795)	721	(683, 784)	-40 (-97, 13)	723	672 876	1053	988 1149	265 (133, 456)

Abbreviations: CHO, Carbohydrates; EI, Energy Intake; Sat Fat, Saturated fat

6.8 Protein distribution

At baseline, the protein intake in the three main meals, i.e., breakfast, lunch and dinner, in EX (control; $n=6$) was 11 (9, 15) g, 20 (10, 24) g and 28 (16, 35) g, respectively. The respective values for EXD (intervention; $n=5$), were 10 (7, 12) g, 15 (14, 16) g and 32 (30, 33) g (**Figure 6.5**). At week16 the protein distribution in the three main meals in EX vs EXD was 9 (8, 11) g vs 10 (6, 13) g in breakfast, 18 (13, 23) g vs 16 (12, 19) g in lunch, and 31 (17, 36) g vs 22 (17, 26) g in dinner, whereas the protein milk was consumed outside these meals and contained 50 g (**Figure 6.6**). Total protein intake was increased by 35 (27, 36) g in EXD.

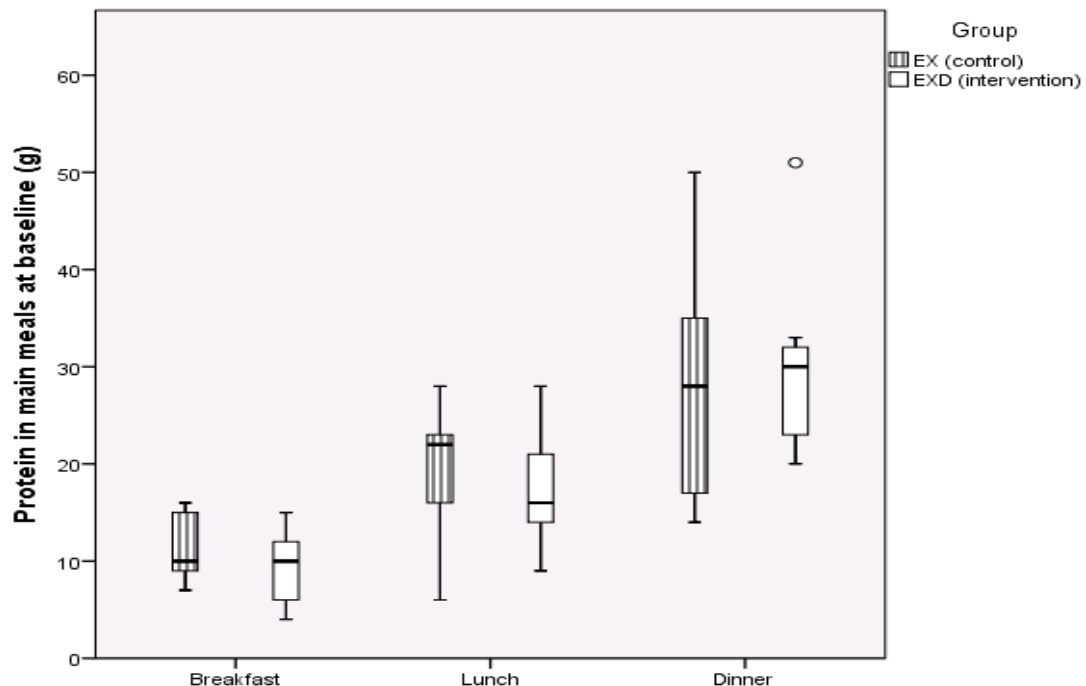


Figure 6.5 Boxplots with baseline protein distribution in main meals for those who completed the study. EX $n=6$, EXD $n=5$.

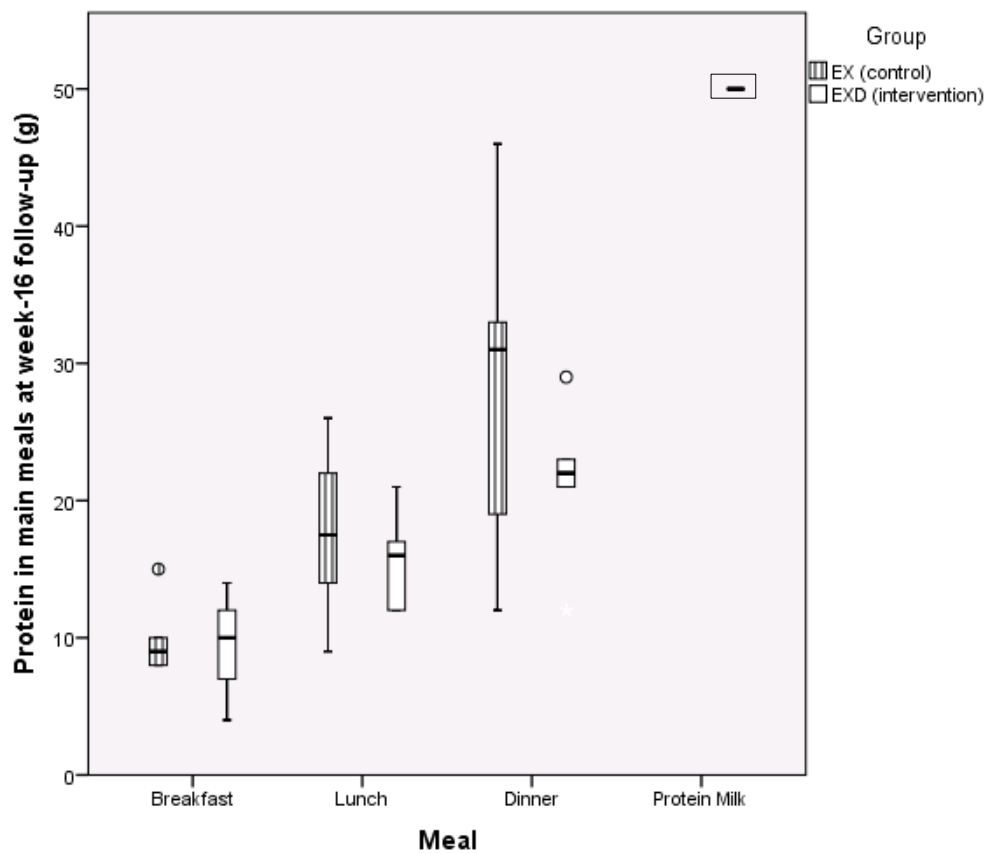


Figure 6.6 Boxplots with protein distribution in the main meals at week16. Notes: The milk supplement (first from the right) had a protein content of 50g and was consumed outside the main meals (either post-workout or pre-sleep) only by the EXD group. EX n=6, EXD n=5.

6.9 Blood markers

Changes from baseline to follow-up for serum 25(OH)D, Insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), urea, creatinine and alkaline phosphatase, along with the reference values (as provided by the microbiology laboratory which conducted the analysis) are presented in **Table 6.11**. At baseline, six out of nine participants exhibited serum (25OH)D concentrations within the reference range ($>50 \text{ nmol L}^{-1}$), except participants no.20 (49 nmol L^{-1} ; EXD), no.53 (48 nmol L^{-1} ; EX) and no.102 (38 nmol L^{-1} ; EX) (**Figure 6.7**). After 16 weeks of supplementation with vitamin D, serum (25OH)D concentrations increased from 57 (43, 72) nmol L^{-1} to 79 (54, 88) nmol L^{-1} in EX and from 67 (53, 108) nmol L^{-1} to 87 (76, 117) nmol L^{-1} in EXD. In terms of individual changes, serum vitamin D (25OH) values increased in nine participants and decreased in two. Participant no.43 (EX) and participant no. 102 (EX) experienced a decline from 83 nmol L^{-1} to 82 nmol L^{-1} and from 38 nmol L^{-1} to 31 nmol L^{-1} , respectively (**Figure 6.7**). After 16 weeks only participant no.102 exhibited levels below the reference cut-off. As reported in more detail in *section 6.11* participant no. 102 discontinued the use of vitamin D tablets half way through the programme (week 8).

All creatinine concentrations at baseline and week16 were within the reference range (**Figure 6.8**). Median (IQR) changes in creatinine were -3 (-4, 0) $\mu\text{mol L}^{-1}$ in EX and -5 (-10, 1) $\mu\text{mol L}^{-1}$ in EXD (**Table 6.11**). Individual serum creatinine levels declined, with two exceptions being participant no.43 (EX group) (increased from 67 $\mu\text{mol L}^{-1}$ to 76 $\mu\text{mol L}^{-1}$) and that of participant no.107 (EXD) which increased from 62 $\mu\text{mol L}^{-1}$ to 64 $\mu\text{mol L}^{-1}$ (**Figure 6.8**).

Table 6.11 Changes in blood markers from baseline to week-16 for EX (control) and EXD (intervention) groups.

		Baseline		Week 16		Reference value/range	Median change (IQR) from baseline to week16	% Median change (IQR) Baseline to week16
		median	IQR	median	IQR			
EX n=5*	25(OH)D (nmol L ⁻¹)	57	(43, 72)	79	(54, 88)	>50	15 (-1, 31)	24.6 (-1.2, 64.6)
	IGF-1 (ng mL ⁻¹)	74	(54, 85)	75	(64, 84)	35-168	0 (0, 14)	0.0 (0.0, 18.9)
	TSH (mU L ⁻¹)	1.3	(0.4, 1.7)	1.1	(0.4, 1.8)	0.35-5.0	-0.1 (-0.1, 0.4)	-5.3 (-12.5, 28.6)
	Urea (mmol L ⁻¹)	4.7	(4.1, 6.2)	5.2	(4.1, 6.1)	2.5-7.8	0.1 (-0.2, 0.4)	2.2 (-5.5, 7.5)
	Creatinine (μmol L ⁻¹)	67	(59, 68)	64	(55, 73)	40-130	-3 (-4, 0)	-4.4 (-6.6, 0.0)
	ALP (U L ⁻¹)	74	(73, 100)	78	(71, 101)	30-130	3 (-3, 5)	4.2 (-3.3, 5.6)
	hsCRP (mg L ⁻¹)	2.0	(0.5, 5.5)	2.0	(0.5, 4.0)	<10	0.0 (-2.0, 0.0)	0.0 (-42.9, 0.0)
EXD n=5**	25(OH)D (nmol L ⁻¹)	67	(53, 108)	87	(76, 117)	>50	19 (9, 27)	31.5 (11.4, 47.7)
	IGF-1 (ng mL ⁻¹)	90	(83, 101)	104	(89, 123)	35-168	11 (-1, 29)	10.1 (-1.1, 32.3)
	TSH (mU L ⁻¹)	1.4	(0.3, 4.4)	1.5	(0.7, 2.1)	0.35-5.0	-0.1 (-1.8, 0.2)	-12.5 (-38.3, 11.9)
	Urea (mmol L ⁻¹)	5.2	(3.0, 6.9)	5.6	(4.0, 8.1)	2.5-7.8	1.2 (0.4, 1.4)	19.4 (3.4, 41.2)
	Creatinine (μmol L ⁻¹)	67	(61, 73)	63	(60, 64)	40-130	-5 (-10, 1)	-6.2 (-13.9, 1.6)
	ALP (U L ⁻¹)	67	(56, 77)	65	(54, 78)	30-130	-4 (-11, 5)	-4.7 (-18.4, 8.0)
	hsCRP (mg L ⁻¹)	1.3	(0.5, 4.3)	0.5	(0.5, 1.6)	<10	-0.8 (-2.3, 0.0)	-30.0 (-67.5, 0.0)

Notes: * it was not possible to collect blood samples from participant no.91 either at baseline or at follow up, therefore, $n=5$ for blood samples in EX. ** one blood sample was collected only at follow up but not at baseline for participant no.5, therefore, in EXD, $n=4$ at baseline and $n=5$ at week-16, respectively. ALP, alkaline phosphatase; hsCRP, high sensitivity C-Reactive protein; TSH, thyroid stimulating hormone

Unlike creatinine, median serum urea increased numerically in both groups, in EX by 0.1 (-0.2, 0.4) mmol L⁻¹, and in EXD by 1.2 (0.4, 1.4) mmol L⁻¹ (**Table 6.11**). At baseline one participant had a serum urea concentration below the reference range, and at the end of the programme, one participant had serum urea above the reference range. In particular, serum urea for participant no. 20 (EXD) increased from 7.4 mmol L⁻¹ to 8.5 mmol L⁻¹ over the course of 16 weeks (**Figure 6.9**).

The median value for insulin-like growth factor-1 (IGF-1) changed from baseline to week-16, from 74 (54, 85) ng mL⁻¹ to 75 (64, 84) ng mL⁻¹ in EX and from 90 (83, 101) ng mL⁻¹ to 104 (89, 123) ng mL⁻¹ in EXD (**Table 6.11**). All individual IGF-1 serum concentrations were within the reference range. Both groups experienced a similar change in thyroid stimulating hormone (TSH) (EX: -0.1 (-0.1, 0.4) mU L⁻¹; EXD: -0.1 (-1.8, 0.2) mU L⁻¹). Median change in alkaline phosphatase (ALP), was 3 (-3, 5) U L⁻¹ in EX and -4 (-11, 5) U L⁻¹ in EXD (**Table 6.11**). Serum high-sensitivity C - reactive protein (hsCRP) remained relatively unchanged in EX [median (IQR) change 0.0 (-2.0, 0.0) mg L⁻¹] and numerically declined in EXD [median (IQR) change: -0.8 (-2.3, 0.0) mg L⁻¹]. Individual serum hsCRP concentrations either remained constant or declined with one exception. Namely, participant no.2 (EX) experienced an increase in hsCRP levels from 2 to 4 mg L⁻¹. All hs-CRP values at baseline and follow-up were within the reference range.

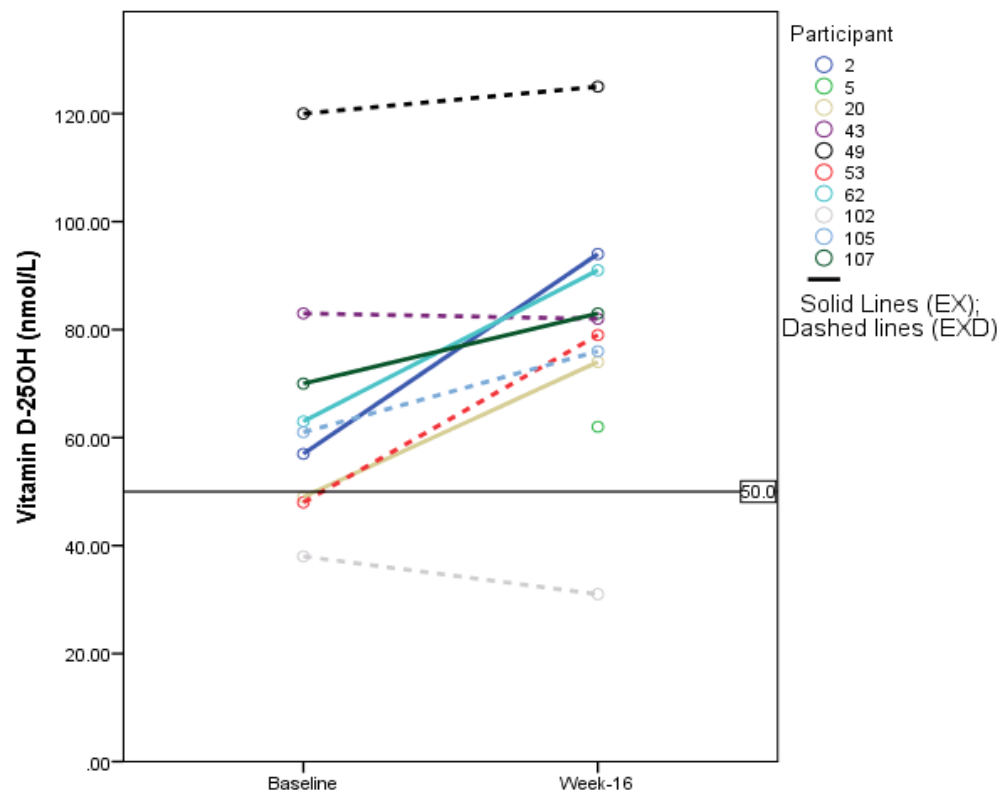


Figure 6.7 Individual changes in serum 25(OH)D concentrations from baseline to week16.
The reference cut-off has been placed at 50 nmol L⁻¹.

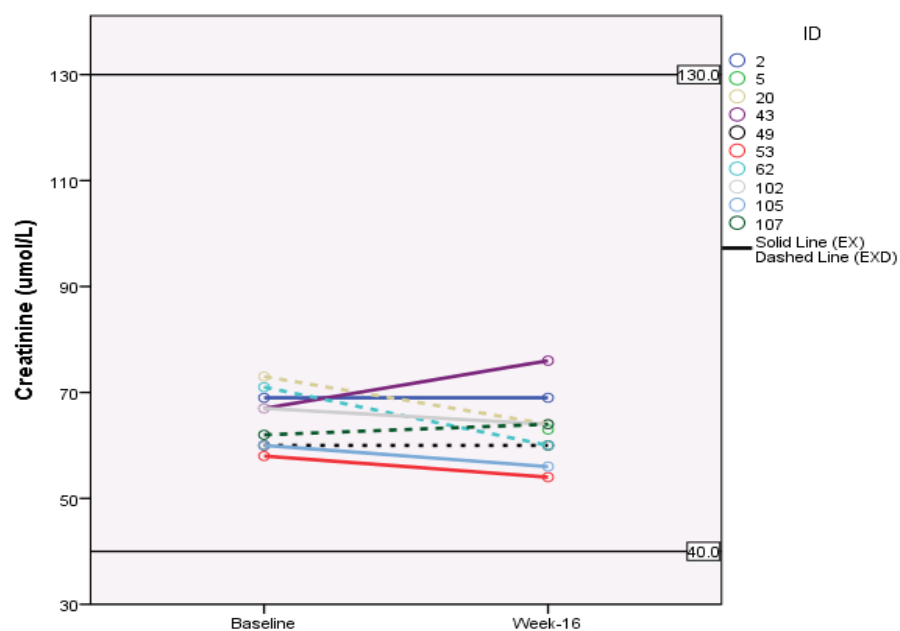


Figure 6.8 Individual changes in serum Creatinine concentrations from baseline to week16. The reference range is 40 – 130 $\mu\text{mol L}^{-1}$.

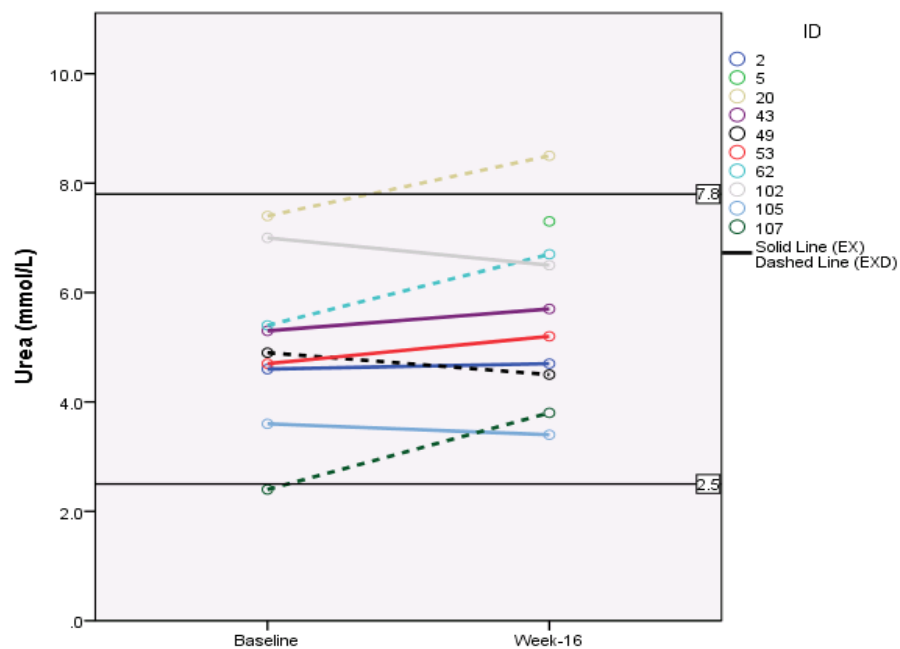


Figure 6.9 individual changes in serum Urea concentrations from baseline to week16. The reference range is 2.5-7.8 mmol L^{-1} .

6.10 Attendance rates and compliance to diet

The total number of exercise classes in the 16 week period was 48. Median (IQR) attendance rate to exercise was 73 (67, 81) %. All individual and group data are presented in **Table 6.12**. The attendance rates to the exercise classes for the two groups were 71 (60, 81) % in EX and 79 (54, 85) % in EXD. Compliance to a) diet and b) consumption of the protein milk supplement in EXD was 80 (70, 87) % and 92 (79, 95) %, respectively.

In general, compliance to diet and milk consumption was good. The main reasons for not adhering to the diet were periods of holidays and social get-togethers, whereas the majority of non-attendances to exercise classes was accounted for by Christmas and Easter holidays (sports facilities were closed for 14 days and four days, respectively, and no classes took place during these periods), social commitments and periods of sickness.

Two participants (no.91 in EX and no.107 in EXD) presented the lowest attendance rates to the exercise classes (**Table 6.12**). For participant no. 91, reaching QMU premises was a challenging task, because commuting via public transport took on average two hours (single direction). Participant no. 107 from EXD was still in part-time employment which allowed her to attend classes usually once or twice a week. Moreover, the same participant reported that adherence to the dietary protocol was not optimal because often her partner was responsible for cooking/preparing meals and additionally, because she liked to attend social events during weekends and/or after work.

Table 6.12 Individual and group attendance rates in exercise classes (%) and adherence to the diet and milk supplement for EXD (intervention group).

Group	Participant #	Age (yr)	Weight (kg)	Adherence to diet (%)	Adherence to milk consumption (%)	Exercise class - Attendance rate (%)
Control	2	74	56.4			68.8
(EX)	43	69	66.2			66.7
n=6	53	73	73.5			79.2
	91	73	59.2			39.6
	102	74	56.4			72.9
	105	75	51.2			87.5
Median (IQR)						71 (60, 81)
Intervention	5	73	104.6	71.4	92.0	66.7
(EXD)	20	67	57.6	91.1	96.4	87.5
N=5	49	68	56.8	79.5	89.3	83.3
	62	77	76.4	83.0	92.9	79.2
	107	65	72.6	68.8	67.9	41.7
Median (IQR)				80 (70, 87)	92 (89, 95)	79 (54, 85)

Notes: All participants are women

6.11 Feedback from participants

With regard to vitamin D supplementation only one participant reported side effects. After eight weeks participant no.102 from EX group expressed concerns that the Vitamin D supplement had triggered a flare-up of gastrointestinal pain that she had been experiencing chronically (due to IBS), therefore, she was advised by the researcher to discontinue the consumption of Vitamin D tablets. The same participant experienced a drop in serum 25 (OH) levels, and remained under the cut-off reference value for 25(OH)D, as presented in *section 6.9*.

One participant from the EXD group commented that consuming one bottle of protein milk every day became an '*uncomfortable necessity*' towards the end of the programme but the fact that she was experiencing positive body composition changes was a strong motivational factor that helped her adhere to the regimen. At the end of week 16 she stated that she was feeling very well and being able to improve her body composition was an invaluable life achievement for her.

At baseline, one participant from EX group reported symptoms of depression and was also concerned that certain family problems would prevent her from taking part in the programme. However, at the end she reported that the programme helped her feel better and she had one of the highest attendance rates (87.5 %). At the start of the study, another participant from the EX group reported that she found great difficulty in performing a simple movement, i.e. to bend down to pick up an item from the floor. At the end of the 16 weeks she was able to fully adopt a correct squatting position without any support and reach the floor with her hands. A participant from the EX group stated that at the end of the trial she was able to take the stairs instead of using a lift without feeling exhausted, which was frequently the case before the trial commenced. She reported that her stamina improved substantially and she was also able to join her friends for outdoor walks, which was something that she was not able to perform prior to the trial, at least without feeling worn out; a feeling that was reported to be very demoralizing. Moreover, she mentioned that she experienced more regular bowel movements, which was a positive change.

Participant no.5 (EXD) reported that before engaging with the programme she was told by her GP that she suffered from impaired fasting blood glucose and she was advised to start exercising. After taking part in the research study she reported that her fasting blood glucose had substantially improved, but no further information was given. In terms of physical function she reported that she was feeling stronger and able to do more everyday activities with less effort. She expressed

how disheartening it was for her to not be able to get up from a soft-cushioning sofa without assistance before the programme. By the end of the study she stated that she was able to rise from any sofas or chairs without any assistance. Additionally, when driving she was unable to turn her head to the side at a 90 degree angle, which was something that she could effortlessly perform at the end of the study, an ability that made her feel more confident in driving.

Participant no.91, who was suffering from osteoarthritis in both hands, reported that the body weight exercises and the elastic bands gave her confidence in performing physical activities better, more effortlessly and with better co-ordination. For her, being able to maintain independence and body functionality was very important since she was also responsible for caring for her husband. Performing daily activities using her hands was challenging and resulted in a progressive decline in engaging with physical activities prior to the study. Although, she did not attend as many exercise sessions as she wanted to, the positive results that she experienced from this programme encouraged her to join an NHS led exercise programme taking place within her local community.

With regard to diet, two participants no.5 and 107 reported that there were periods during this study which they were not feeling satiated during the day and wanted to snack more or increase their portion sizes. Moreover, participant no.107 reported that since her partner was often responsible for cooking and food preparation, it was difficult for her to adhere strictly to the regimen. Participants no.62 and 107 asked for some alcohol to be regularly allowed in their diet so that they can socialize with peers and family. They were advised that they could have a small glass of wine or small bottle of beer (330 mL) three times a week, but it should be complementing it with regular sips of still or sparkling water. Participants no.20, 49 and 62 expressed positive comments about the diet and did not find it a challenging task to adhere to it. Apart from participant 49, the rest of EXD group found that switching between the different flavours of the protein milk

supplement encouraged them stick to the protocol. After this research study was concluded, participants who were keen to continue with an exercise programme were advised to visit appropriate settings at close proximity to their home. In addition, some participants wanted to keep exercising at QMU premises, therefore an exercise class for the over 60s was created at QMU sports centre for older adults who want to exercise on a regular basis, and it is now also open to the general public. At the end of the trial, there was a presentation delivered to all participants, in the form of an educational session, so that they could all receive information about healthy eating. Emphasis was placed on consuming at least five portions of fruits and vegetables every day, have balanced meals with adequate protein and healthy unsaturated fats, and how to limit the consumption of free sugars.

6.12 Summary

In summary, after 16 weeks the high-protein hypocaloric diet resulted in weight loss in EXD [median (IQR) change: -5.0 (-5.0, -6.8) kg], which was driven mainly by loss of fat mass [-4.7 (-4.8, -4.2) kg]. A numerical increase in skeletal muscle mass was noted in EX [0.5 (0.3, 0.7) kg], and a maintenance in EXD [0.1 (-0.4, 0.7) kg]. Both groups improved their strength and physical function. Mixed results were obtained for quality of life, with the most noticeable numerical change being an increase in both groups in perceived health compared to previous year by 25 (0, 25) points. Serum 25(OH)D increased in nine participants, and decreased in two, one of which had stopped taking the vitamin D supplement half-way through the programme. The higher protein intake in EXD (intervention) group did not appear to negatively affect serum creatinine.

Chapter 7. Discussion: Sarcopenic obesity in Scottish older community-dwellers. A cross-sectional study.

7.1 Sarcopenia and sarcopenic obesity in Scotland: a comparison with the rest of the UK and world.

This is one of the first studies to assess sarcopenia and sarcopenic obesity rates in Scottish older independent-living community-dwellers. In the present study the overall prevalence of sarcopenia was 14.8%, and of sarcopenic obesity 4.6% based on a BMI ≥ 30 kg m⁻² or alternately, 12.0% based on increased body fat ($\geq 28\%$ in men and $\geq 40\%$ in women). As discussed in this chapter these results are in agreement with the published literature (Cruz-Jentoft et al. 2014), however the scarcity of studies in this area (particularly in Scotland and the UK), combined with the lack of standardized operational protocols, as well as the plethora of definition criteria, render a direct comparison of prevalence rates across studies quite challenging. Nevertheless, the findings of the present study are discussed and compared with the most relevant data from studies on sarcopenia and sarcopenic obesity rates.

7.1.1 Sarcopenia

In the present study only one method for the detection of sarcopenia was used, in agreement with EWGSOP, however a plethora of different cut-offs exists (Cruz-Jentoft et al. 2010). In a recent study of 965 German men (≥ 70 years) in Germany, the rates of sarcopenia prevalence (defined using a local reference group of n=1189 young men) were 4.9% based on the EWGSOP criteria and 3.8% based on the IWGS criteria (Kemmler et al. 2017a). In addition to these two, another recently introduced diagnostic method was applied, developed by the Foundation National Institution of Health (FNIH; Studenski et al. 2014). The FNIH uses fixed cut-off scores for

handgrip strength (<26 kg in men and <16 kg in women) combined with an index of low lean mass normalized for BMI (low appendicular lean mass \cdot BMI⁻¹ <0.789 in men and <0.512 in women) (Studenski et al. 2014). Based on the FNIH criteria, the prevalence of sarcopenia in the same cohort of German older adults was 3.7%. Although there were not large differences in the prevalence rates derived from the three methods (4.9%, 3.8% and 3.7%), the actual overlap of these definitions was moderate at best (36%-47% overlap). That is, people who were classified as sarcopenic based on one method had less than a 50% chance of being diagnosed with sarcopenia based on another. The findings of that study agree with those of a previous trial that included 1,325 women (Kemmler et al. 2016). That study reported that sarcopenia prevalence ranged from 3.3% (IWGS) to 4.5% (EWGSOP) but the overlap between the two was again moderate, with only 20 women being defined as sarcopenic by both methods (~33-45% overlap). The authors suggested that this discrepancy is likely to be accounted for by the different muscle mass cut-offs and the diagnostic tests employed in each methodology (e.g. gait speed vs handgrip).

In the current study, the rates of sarcopenia (13.8% in men and 15.2% in women) were higher than those of Kemmler et al. (2016) and Kemmler et al. (2017a), whereas prevalence of low muscle mass alone, was alarmingly high at 62.1% in men and 36.7% in women. However, the reference cut-offs used in the current study, were fixed and derived from a US rather than a young adult Scottish population cohort, whereas those of Kemmler and colleagues were derived from local young adult healthy groups. Additionally, the sample size was relatively small, and as such, it cannot be corroborated whether it reflects the true sarcopenia rates for the whole population of Scottish community dwellers over the age of 65 years. It is however, surprising that approximately three out of five men and two of five women had a muscle mass below the reference values, even though many of them were 'young old', that is 65-74 years old (Zicca et al. 2009) and not physically weak as discussed later.

In a UK study, Patel et al. (2013) examined the prevalence of sarcopenia in English older adults from the Hertfordshire Sarcopenia Study (HSS) and the Hertfordshire Cohort Study (HCS). The reported rates in men were again lower than those of the current study, 6.8%-7.8% in HSS, and 5.0% in HCS. In a cohort of older English women (n=1,022, mean age 67.1 years from the HCS cohort; Patel et al. (2013).), sarcopenia rates were ~8%, still lower than the rates noted in Scottish women in the current study. Similar to the present study, Patel et al. (2013) used the EWGSOP criteria for sarcopenia, however, muscle mass was measured by anthropometry (skinfolds), which may account for some of the differences noted in the two studies. A trial including the HCS cohort of English older adults compared the rates of sarcopenia using DXA for body composition analysis, and three different diagnostic criteria; the EWGSOP, IWGS and FNIH, and noted prevalence rates of 3.3%, 8.3% and 2.0%, respectively (Clynes et al. 2015). Therefore, even in the same population cohort, different criteria can potentially affect the outcome. However, it should be noted that although the studies by Patel et al. (2013) and Clynes et al. (2015) are not in absolute agreement, on average they report prevalence rates lower than the ones from the current study. Another trial from the UK in hospitalised older patients reported prevalence rates of sarcopenia of ~10 % (Gariballa and Alessa 2013), whereas in COPD patients the rates have been reported to be somewhat higher (15%) (Jones et al. 2015a), and similar to the current ones. Only Dodds et al. (2017) have reported higher prevalence rates in the UK than the present ones, with 21% of participants (149 out of 719) diagnosed with sarcopenia. However the mean age of participants in that study was 86 years, which is substantially higher than the median age of participants in the current study [70 (67, 75) yr].

Based on these findings it could be hypothesised that the prevalence of sarcopenia is higher in Scottish community dwellers compared to the rest of the UK or other parts of Europe. Since

sarcopenia diagnosis was based on low muscle mass and low strength, for such hypothesis to be corroborated it would require a) the Scottish older adults to have lower muscle mass and strength than their counterparts, and/or b) BIA to systematically underestimate the amount of muscle mass, resulting in consistently lower muscle mass and higher prevalence of sarcopenia. In the current cohort the median value of hand grip in men was 42.5 kg, which is in good agreement with the national average for the same age group (39-43 kg; Dodds et al. 2014), but lower than the one from the HCS cohort (43.9 kg; Patel et al. 2013) and higher than that by Kemmler et al. (2017a) (36.2 kg). Similarly, women's strength in the current study (23.5 kg) was in good agreement with the mean value from the study with German women (23.4 kg) (Kemmler et al. 2016), and with the national average (24-25 kg) (Dodds et al. 2014). Regarding BIA validity, it has been previously discussed that BIA is in relatively good agreement with DXA for assessing body composition (Ling et al. 2011), and therefore, is not likely to account for the high rates of low muscle noted in the current study. In fact some studies have shown that, if anything, BIA may overestimate the amount of skeletal muscle mass when compared against DXA (Beaudart et al. 2015; Buckinx et al. 2015), which may theoretically result in consistently lower prevalence rates of sarcopenia and not higher. In terms of skeletal muscle mass *per se*, there is currently a scarcity of data, since most studies have used lean mass (appendicular or total) as a surrogate for muscle mass (Patel et al. 2013; Clynes et al. 2015) or mid-arm muscle circumference (Gariballa and Alessa 2013). Only Jones et al. (2015a) and Dodds et al. (2017) used a BIA-derived skeletal muscle mass value to assess sarcopenia, and the indices obtained from 85+ years old adults (SMI: 9.90 kg m⁻² in men and 7.70 kg m⁻² in women) and COPD patients (SMI: 9.61 kg m⁻² in men and 6.93 kg m⁻² in women) are very similar to the ones noted in the current study (*section 5.1.1*). This finding suggests that the current cohort was actually characterised by low muscle mass. Whether the latter hypothesis can be generalized for the whole older population of Scotland will need to be confirmed in future studies. However, as discussed in more detail in *section 7.1.3*, it is proposed that this may

be part of a wider health problem in Scotland that has been long identified, and has been linked to higher mortality rates (Leon et al. 2003).

In other European studies, the rates of sarcopenia prevalence have been reported to be similar or even higher than these of the current study; for instance in Belgium, albeit in oldest old adults (mean age 85 years), the average rate of sarcopenia diagnosis in both sexes (n=103 men and n=185 women) was 12.5% (Legrand et al. 2013). In the Netherlands sarcopenia was present in 17.4% of a cohort of older Dutch men (n=450) and women (n=434) (Bastiaanse et al. 2012). In a cohort of older Spanish community-dwellers (mean age 75 years) prevalence rates were 10% in men and 33% in women (Masanes et al. 2012). One of the highest rates of sarcopenia has been reported by researchers in Italy, with 67.7% of men and 20.8% of women, being defined as sarcopenic (Landi et al. 2012). The latter study was however conducted in a cohort of older adults residing in nursing homes (n=121, ≥ 70 years). In general, according to a systematic review by Cruz-Jentoft et al. (2014) prevalence of sarcopenia may range from 1-30% in community dwellers, and is expected to be somewhat higher in long-term institutionalized adults, ranging from 14% to 33%. According to Kemmler et al. (2017a), socio-economic and lifestyle differences between population cohorts may generate a strong confounder not only when comparing prevalence of sarcopenia in neighboring countries, but even within the same country. Such factors may include but are not limited to, income, education, deprivation index, access to healthcare, unemployment rates, and neighborhood/district (Mello et al. 2014; Kemmler et al. 2017a). However, this kind of information was not collected in the current study.

With regard to gender differences the present study noted that although low muscle mass was observed in the majority of men (62.1% vs 36.7% in women), when handgrip was also taken into account, sarcopenia rates were reversed with more women being diagnosed as sarcopenic than

men (13.8% in men vs 15.2% in women). The fact that the two genders were not represented in equal numbers and men were mostly ‘young old’ (compared with women whose age was more evenly distributed across the cohort) may account to some degree for these differences. Studies have reported that sarcopenia may affect men more than women (Landi et al. 2012; Clynes et al. 2015), however the study by Patel et al. (2013) argued for the opposite. According to the systematic review by Cruz-Jentoft et al. (2014), a consistent pattern in differences between genders is not evident and depends on the population cohort. In general, the topic of gender differences in predisposition to sarcopenia is not very easy to approach. In fact, one study reported that men \geq 65 years may be affected more from sarcopenia than women of the same age, but the pattern seems to reverse in those over > 85 years, with women experiencing higher rates of sarcopenia (Yamada et al. 2013). Thus, it is apparent that generalisations may not be prudent, as this is a very complex issue. An anecdotal observation from the current study was that the majority of men who attended the screening phase considered themselves physically ‘fit’ and were either seeking for more information about their body composition and strength status, or were encouraged to join the study by their partners. Therefore, it could be speculated that even if the muscle of men had atrophied over the years, they had maintained their physical function and strength through participation in physical activities, which would also explain the fact their handgrip was not lower than the national average.

Besides obvious sources of discrepancy such as different diagnostic criteria and cut-offs, gender, age and ethnicity, a very recent study also highlighted the fact that the measurement tools can account for large differences between studies (Beaudart 2015). The authors stated that there may be up to a 2-fold difference between sarcopenia prevalence rates obtained using a pneumatic handgrip dynamometer vs a hydraulic one, even after calibration. Namely, the prevalence rates were 22.4% with a pneumatic dynamometer, as opposed to 11.4% with a hydraulic, which were

used to measure the strength of the same individuals, using the same criteria, methodologies and cut-offs. Another important factor to consider is that it was not until recently that studies included assessment of the performance of the different sarcopenia definitions in predicting physical disability and adverse health outcomes in older adults (Bischoff-Ferrari et al. 2015; Clynes et al. 2015; Schaap et al. 2015), and their findings are so far conflicting. Therefore, it has not been corroborated which definition of sarcopenia is the most valid at predicting changes in health status, and as such, the main criteria for selection of a methodology are availability of resources, affordability and types of studies (e.g. field vs clinical/ lab based). Based on all the above facts the utility of sarcopenia prevalence (and consequently sarcopenic obesity) is currently questionable. This emphasizes more the need for universally adopted diagnostic criteria and simplification of the operationalisation process.

7.1.2 Obesity

According to the latest Scottish Health Survey, mean BMI has increased across all adult age-groups since 2003 from 27.1 kg m⁻² to 27.7 kg m⁻², and obesity alone (BMI ≥ 30 kg m⁻²) affects approximately 36% of the overall Scottish population aged 65-75 years (41% in men and 32% in women) (Scottish Government 2016a). These figures report obesity rates based on the BMI classification, however, no large-scale data have been reported in Scotland based on body composition indices, such as % body fat. In the current study, the obesity rates based on BMI were 24.1% in men and 29.1% in women, which are lower compared to the Scottish average. This can be mainly attributed to the fact that participants were young old free-living community dwellers. In addition, participants of the current study were resident in areas of Scotland with a diverse deprivation index (Scottish Government 2016b). Obesity rates have been associated with the index of deprivation, with a ~10-20% difference in BMI-assessed obesity rates observed between

Scottish cohorts of different SIMD quintiles (Scottish Government 2016a). However, some rather conflicting results have also been presented, with those from the second highest deprived areas reporting higher obesity rates than their counterparts from the highest deprived areas (Scottish Government 2017), which suggests that factors other than deprivation may play an important factor.

According to % BF classification, obesity rates in the current study were approximately 2-fold to 2.5-fold higher than the BMI-derived prevalence rates. Namely, 41.4% of men (vs 24.1% by BMI) and 70.9% of women (vs 29.1% by BMI) were diagnosed with obesity based on the body fat cut-offs. This finding agrees with published data showing that obesity rates may be substantially higher if body composition is used as a proxy for obesity instead of BMI (Kemmler et al. 2016; Kemmler et al. 2017a). In the study with older women prevalence of obesity based on BMI > 30 kg m⁻² vs prevalence based on % body fat (> 35%) was 19.8% vs 63.6%, respectively (Kemmler et al. 2016). Obesity prevalence rates in men were 63.3 % (for a %BF > 28%) vs 19.9 % (for BMI > 30kg m⁻²) (Kemmler et al. 2017a). Although the magnitude of the differences in prevalence between BMI and BIA values cannot be reliably applied to the national averages, if it is hypothesised that there is at least a 2-fold difference between BMI-derived and % body fat-derived rates, then the real prevalence of obesity in Scottish older adults may be even greater than 70%. The implications of the discrepancies between obesity rates is discussed in detail in *section 7.1.4*.

7.1.3 Sarcopenic Obesity

Interpreting findings on sarcopenic obesity is even more complex compared with the two conditions alone. In the current study, an approximate 3-fold difference was demonstrated between the prevalence rates of sarcopenic obesity obtained by two different methods (Chapter 5 Results,

section 5.1.1). If more diagnostic criteria were used also for sarcopenia perhaps the difference would be further amplified. Batsis et al. (2013) has shown how variable the prevalence rates of sarcopenic obesity can be depending on the definition criteria and the assessment methods. In fact, they suggested that prevalence rates may differ by 19-fold in men and 26-fold in women, ranging from as low as 3% to as high as 96% depending on the definition criteria, and assessment methods used, as well as due to real differences related to population characteristics (e.g. age, gender and ethnicity). Similar to the present study, the two studies by Kemmler and colleagues (Kemmler et al. 2016; Kemmler et al. 2017a) aimed to examine these discrepancies and obtained similar results; that is, a ~2.5-fold difference between the sarcopenic obesity rates was detected when obesity was defined as high BMI vs high body fat.

The heterogeneity in the diagnosis of sarcopenia, obesity and sarcopenic obesity (apart from real differences between different population cohorts) can be accounted for by various reasons. Firstly, there are different adiposity and muscle mass indices (BMI, %FM, WC, Fat mass index, SMI, ASMI, $SMM \cdot FM^{-1}$, $ALM \cdot BMI^{-1}$). Secondly, the determination of cut-offs has been based on quartiles, quintiles, fixed cut-offs based on regression analysis data and T-scores (2SDs below the average of a young/healthy population). Thirdly, there are different body composition assessment protocols (DXA, BIA, MRI, CT, ADP, skinfolds), and finally, even when similar protocols are employed the use of different assessment tools (e.g. pneumatic vs hydraulic dynamometer) may account for the discrepancies (Prado et al. 2012; Siervo et al. 2014; Beaudart 2015). Given the complexity of the assessment methods, it is not surprising that studies show that the prevalence of sarcopenic obesity may vary from 0% to 100%, even in the same population cohort when different diagnostic criteria/protocols are used (Johnson-Stoklossa et al. 2017). This highlights the necessity for a single universally adopted operational definition, which should become the first priority since sarcopenia and obesity are particularly important for our swiftly-ageing societies.

In a preliminary study in a smaller cohort of Scottish older men and women ($n=59$, ≥ 65 years, independent living community dwellers and sheltered-housing residents in Lothian), 27 out of the 59 screened (46%) were diagnosed with sarcopenia, and 21 of them were sarcopenic obese (36%) (Jones et al. 2015b). Although the rates of sarcopenia and sarcopenic obesity were higher than in the current study (perhaps because participants in Jones et al. (2015b) were older with a mean \pm sd age of 81.1 ± 7.2 years, and not all of them were independent-living dwellers), that study provides a relatively good comparison with the current one since the diagnostic criteria and assessment protocols were similar. However, some small differences were noted, e.g. Jamar dynamometer in Jones et al. (2015b) vs Takei in the current. The differences in prevalence rates underlines that even in cohorts from the same population source (in this case older adults from Lothian, Scotland) substantial differences can be observed. Although the study suffered from the same limitation as the current study, that is, the small sample size, it agrees with the previous hypothesis, and perhaps stresses it to a higher degree, that Scottish older adults may have lower muscle mass compared to their counterparts from the rest of the UK, and possibly other countries of the Western Europe.

The characteristics of the current cohort were similar to Scottish national averages, that is, BMI was not significantly different than the Scottish average, and the proportion of participants with a normal, overweight and obese BMI was comparable to the national averages (15%, 44%, and 35%, respectively) (Scottish Government 2017). It could therefore be assumed that even though the current cohort size was small, it offers a relatively good representation of the Scottish older community-dwellers. Although the current study only provides a ‘snapshot’ of the current body composition status of Scottish adults, other published findings show that in the past years fat mass and particularly abdominal fat has been increasing disproportionally to muscle mass in Scottish older adults, and especially in women (Lean et al. 2013). It is also known that Scottish older adults

have higher average BMI, body weight, and waist circumference compared to their English counterparts (NHS National Archives 2016; Scottish Government 2017). Moreover, inflammatory responses increase with age in Scottish adults, and average blood hs-CRP concentrations in Scotland appear to be higher than England (Scottish Government 2012; Zheng and Xie 2017). Therefore, it is hypothesised that the low muscle mass findings of the current study may be part of a bigger issue that has been long identified, and has been termed ‘the Scottish effect’, which refers to Scotland as the ‘sick man of Europe’ (Leon et al. 2003; Minton et al 2017). Scotland has higher cancer, CVD, CHD, stroke, alcohol, drug-related mortality, and overall mortality rates than the rest of the UK but also the rest of Western Europe, and the gap continues to widen (McCartney et al. 2015; Bhatnagar et al. 2016; Minton et al. 2017). Perhaps it is the result of a chronic accumulation of stress and inflammation due to several reasons (e.g. unemployment, deprivation, alcohol misuse, low fruit and vegetable consumption, smoking) that may account for this phenomenon, at least to a certain extent (Leon et al. 2003; Hughes et al. 2015), which may also explain this shift towards higher body fat and lower muscle phenotypes. However, differences in deprivation and socioeconomic factors only explain some of the variability in mortality rates. In fact, even when adjusting for socioeconomic factors, Scotland still has higher CVD, cancer, and overall mortality rates than the rest of the UK and Western Europe (Bhatnagar et al. 2016). Recently, it has also been shown that muscle atrophy in older adults can increase mortality risk (Santanasto et al. 2017). This finding combined with the suspected low muscle mass of Scottish older adults, would indeed provide an additional factor that could explain some of the variability in the higher mortality rates in Scotland. The question is whether low muscle mass is actually prevalent in Scotland and this combined with increased adiposity *per se* leads to increased mortality; or perhaps it is the general lifestyle and other factors (e.g. age, sex, ethnicity, genetic/biological factors, psycho-cognitive status), that may promote deterioration of body composition

and increased mortality rates. In either case, it underlines the necessity for immediate actions in Scotland and more studies to explain this phenomenon.

7.1.4 Importance of body composition in older age and implications of different classification criteria

In Scotland, long-term conditions are responsible for 80% of GP consultations and for over 60% of all cause-mortality (Scottish Government 2009). The prevalence of such conditions can range from 21% in young adults to 60% in those older than 75 years, with the steepest increase in health conditions occurring between the 65-74 years group and the 75+ group (from 45% to 60%, respectively) (Scottish Government 2016a).

Despite the fact that obesity can promote adverse health events, its definition and operational diagnosis in older adults has not been robustly established, which can have a subsequent effect on the diagnosis of sarcopenia and sarcopenic obesity. Although BMI can predict the risk of disorders such as CVD and type II diabetes, its sensitivity especially in older age is only modest, predominantly due to its inherent inability to distinguish between the two main body components, that is, fat mass and lean mass (Ashwell et al. 2012; Siervo et al. 2014). In the current study, it was evident, especially in women, that high fatness can be present even at normal or overweight BMIs. This is in agreement with Koster et al. (2011) and Sahillary et al. (2016) who reported that a mean BMI of $\sim 27 \text{ kg m}^{-2}$ in older adults corresponds to a mean % body fat of $\sim 28\%$ in men and $\sim 42\%$ in women. Moreover, making assumptions on health risks based on BMI may affect the interpretation of data, since within any given BMI category there may be older adults with increased body fatness (also supported by Stokes 2014), which would directly imply lower lean mass. In fact, the only participant in the current study with a BMI below 18.5 kg.m^{-2} had a % body

fat > 40%, which was, unsurprisingly, accompanied by a very low muscle mass. However, most studies to date have been observational and therefore, cause and effect cannot be determined. This highlights the importance of measuring not only body composition but also the ability of certain cut-offs to predict changes in function and morbidity/mortality rather than simply reaching conclusions based purely on body size from observational studies (Berrigan et al. 2016).

The present study showed a 2-fold difference in the prevalence of high adiposity based on BMI vs %BF. This is in agreement with Okorududu et al. (2010) who noted that a BMI of 30 kg.m⁻² can misidentify high body fatness in > 50% of the cases in older adults, which then profoundly underestimates the true prevalence of obesity. Therefore, the use of BMI as an obesity surrogate in older age can lead to a serious underestimation of obesity and subsequently sarcopenic obesity diagnosis (Newman et al 2003a; Kemmler et al. 2016). In fact, it has been suggested that the ideal BMI cut-off in older adults is 25 kg m⁻², since a BMI of 30 kg m⁻² carries a very low diagnostic accuracy and sensitivity, and the majority of older adults are likely to exhibit high adiposity if body fatness is assessed based on %BF (Batsis et al. 2016).

Newman et al. (2003a) suggested that BMI is associated with fat mass, lean mass and lean mass adjusted for stature ($LM \cdot height^{-2}$). In fact, absolute lean mass is likely to be higher in an obese individual than their lean counterpart since weight gain leads to an increase in both lean and fat mass (Newman et al. 2003a; Muller et al. 2016). Newman et al. (2003a) reported that using lean mass adjusted for stature as a surrogate for sarcopenia leads to low likelihood of overweight and obese individuals be diagnosed with sarcopenia. That is, in high BMIs even if muscle is 'normal' either in absolute amounts or relative to stature, it may be low in relation to fat mass. For these reasons, some scientists have gone as far as characterising the use of BMI in older age as 'absurd', especially when focusing on conditions such as sarcopenia and sarcopenic obesity (Kemmler et

al. 2017a). Considering that BMI is perhaps the most frequent tool used in primary health settings, this questions the need to re-evaluate the importance of body composition changes in older age and how these can be diagnosed in practice.

The present study has shown that the use of BMI and % body fat may result in different phenotypes in terms of muscle mass and strength between those who are obese vs non-obese counterparts. Namely, muscle mass in the obese group was higher than the non-obese based on BMI, however, when %BF was used to define obesity, the opposite pattern was observed, with the non-obese having higher muscle mass, as well as strength compared to the obese group. This has also been implied by Newman et al. (2003a), who reported that the use of BMI can mask sarcopenia since individuals with higher BMIs are likely to have higher absolute (or adjusted for stature) muscle mass due to their high overall mass. For example, a person weighing 100 kg out of which 30 kg are muscle mass, will have a higher muscle mass or muscle index ($\text{muscle mass} \cdot \text{height}^{-2}$) than a counterpart of similar age and height, with a 50 kg bodyweight and 25 kg muscle mass. Recently, a study with 674 women >65 years old assessed differences in muscle mass index between participants with obesity (based on BMI) and their normal-weight counterparts (Muscariello et al. 2016). Their findings are in agreement with the current study, demonstrating that the obese group had a significantly higher muscle index compared with the non-obese (9.3 kg m^{-2} vs 8.1 kg m^{-2}). However, the same comparison was not conducted based on % body fat classifications, nor were strength data presented, which would offer a direct comparison with the present study. Nevertheless, muscle mass index was assessed via bioelectrical impedance analysis in the study by Muscariello et al. (2016), in addition to using also the same prediction equation as in the present study.

The impact of the use of BMI on muscle mass phenotypes has been also observed by Graf et al. (2016), who assessed the prevalence of low muscle mass in 3,122 older German individuals. It was reported that those with higher BMIs ($>25 \text{ kg m}^{-2}$) were less likely to be identified with low muscle mass compared with their eutrophic counterparts (Graf et al. 2016). This may have wider repercussions, for instance, limiting the pool of potential participants with sarcopenic obesity, conflicting interpretation of research findings (e.g. the ‘obesity paradox’), or incapacity to compare the effectiveness of intervention strategies. Similarly, Beaudart et al. (2015) suggested that if the clinical characteristics and phenotypes in older adults are different depending on the tools or methodologies used, then the long term health consequences of body composition-related conditions may differ, and as an outcome will be challenging to evaluate the effectiveness of therapeutic strategies.

In the current study, the associations between muscle quality and body weight, absolute fat mass, and sagittal abdominal depth (SAD), were all significant (*section 5.1.3*). In terms of SAD, there are no other studies showing a direct relationship between muscle quality and SAD *per se*, and this finding could be further examined mechanistically in larger cohorts. It can be hypothesised that this relationship could be partly an indication of increased myosteatosis (Reinders et al. 2016) and/or mediated by pro-inflammatory agents (Beasley et al. 2009; Zoico et al. 2010). Reinders and colleagues reported that intermuscular and intramuscular fat deposition can be deleterious for muscle quality, and more importantly, for every SD-increment in myosteatosis the mortality risk can increase by 13-23%.

The assessment of muscle quality in the current study was based on handgrip strength and not on a weight-bearing strength exercise, therefore, in theory fat mass should not be a confounder. However, fifteen individuals exhibited poor muscle quality (lower than the 25% percentile) even

though they had an adequate amount of muscle mass and were not sarcopenic. The most characteristic example was participant no. 44 who had a high amount of absolute muscle mass but low muscle quality. Therefore, it is suggested that fat tissue can account for some of the variance in muscle quality. In the current study, this appeared to be relevant especially in men since it accounted for 24% of the variance in muscle quality. This could be partly accounted for by gender differences, such as visceral adiposity, which appear to be more pronounced in older men than women of similar age and body composition (Beasley et al. 2009). As reported in Chapter 1, visceral adiposity is particularly associated with cytokines production that may negatively affect indices of sarcopenic obesity, such as muscle mass and strength.

The relationship between fat mass and muscle quality has also been examined in other studies. Vilaca et al. (2014) used a %BF >38% as a surrogate for obesity in 75 Brazilian older women (65-80 years old) and found that the obese women had significantly lower muscle quality compared with their eutrophic counterparts. Muscle quality, however, was measured as strength standardised for lean mass in the respective limb (e.g. handgrip strength over arm lean mass or knee extension over leg lean mass). Such measurements were not feasible in the present study due to technical limitations. Koster et al. (2011) examined data from 1,178 women and 1,129 men from the Health, Ageing and Body Composition study (ABC study) cohort. At baseline, one standard deviation of fat mass was associated with 1.3 kg and 1.5 kg more lean mass in men and women, respectively. However, when lean mass was normalised (i.e. adjusted) for body weight (lean mass \cdot body weight⁻¹), a higher fat mass was associated with a lower lean mass (normalized), in both sexes. Moreover, those with higher fat mass at baseline experienced the steepest losses in lean mass after three years follow up (approximately 0.2 kg of leg lean mass was lost per year).

Using data from the same cohort of older adults (the ABC health cohort), Newman et al. (2003b) conducted further analysis aiming to determine the % body fat characteristics of older men and women for optimal muscle quality. Their findings indicated an inverted U-shape relationship between muscle quality and body fatness, with very low or very high levels of % body fat exhibiting the lowest muscle quality, whereas at body fat ranges of ~ 16% - 22% in men and 26% - 34% in women, muscle quality was optimal. However, despite the significant association between muscle quality and body fat, which is consistent with the current study, Newman et al (2003b) proposed that other factors, such as the proportion of muscle fibre types, increased connective tissue with advancing age, and altered muscle metabolism may also account for some of the variation in muscle quality.

Therefore, it can be proposed that it is not only the absolute amount of muscle or fat mass, but also factors, such as the relative contributions of the different tissues, that can play an important role in older age. Indeed, the ratio of visceral fat to thigh muscle area assessed by computed tomography (CT) has been shown to be associated with an increased risk of metabolic syndrome in the Korean Sarcopenic Obesity Study (KSOS; Lim et al. 2010). On a similar note, a higher ratio of lean mass to fat mass has shown association with a lower likelihood of functional impairments and a higher gait speed, in 1,655 older adults (Sternfeld et al. 2002). The ratio of lean mass to fat mass can also predict a 4-year risk of physical disabilities, as demonstrated in a study with 3,153 Chinese older adults (Auyeung et al. (2013). These findings highlight that apart from the absolute amount of fat mass, fat distribution and the relative proportion of fat to muscle mass also play a vital role. In fact, new models have emerged, suggesting that body composition assessments should take into account the health impact of both adipose tissue and lean mass within an individual. One such paradigm is the metabolic-load and metabolic-capacity model proposed by Siervo et al. (2015), which proposes that health risks should be estimated based on the relative

contribution of the two key components, fat mass (total and truncal) and lean mass, to physiological functions.

Considering that overweight/obese adults will usually receive advice, such as embarking on a weight loss diet and increasing physical activity levels (NICE 2014) based on their BMI, it is plausible to assume that if BMI lies within the normal range they are not likely to be encouraged to change lifestyle practices, especially since the majority of GPs are still unfamiliar with the PA and health guidelines, or they do not have the time to engage in relevant consultations (Chatterjee et al. 2017; Cottrell et al. 2017). Not only that, but to date specific guidelines exist for undernourished older adults, obese adults, older institutionalised adults, and those with recurrent falls (NICE 2014; GOV UK 2017; NICE 2017), but not for independent-living dwellers who perhaps fall between normal overweight BMI ranges, some of who may be sarcopenic and/or obese based on a high % BF. In the current study there were cases of adults with a high %BF, but within a normal BMI range, who stated that clinicians have never discussed with them about body composition during older age, nor provided them with specific guidelines for diet and exercise, that may help them sustain or increase their muscle mass while promoting fat losses. On the other hand, those individuals with an increased BMI who will be advised to start a weight loss regime, without taking into consideration the amount of lean mass, the ratio of fat to muscle or distribution of fat, may jeopardize their health. This type of advice may be detrimental for the physical and overall health status of older adults who may be suffering from undiagnosed muscle atrophy (Johnson-Stoklossa et al. 2017). From a public health perspective, if sarcopenia and sarcopenic obesity are not detected at an early stage (ideally early detection during a visit to the GP), then the resultant impact on health may not be identified until at a late stage when sarcopenic obesity is established, and/or hospitalization is required. Hospitalisation and low physical activity can reduce muscle mass by ≥ 1 kg following as little as five days of bed rest (Ferrando et al. 2010; Dirks et al.

2017), which is very probable given that the average length of stay in hospital is one week (Eurostat 2017). Apart from the direct effect of reduced activity/hospitalization on muscle atrophy, the issue may become even more complex considering that neither muscle mass nor its ability to uptake and utilize glucose are likely to return to pre-admission levels, resulting in impaired glucose tolerance (McGlory et al. 2017). Additionally, even if physical activity and dietary patterns return to normal, MPS rates are likely to remain lower compared with pre-hospitalisation (McGlory et al. 2017). That is, failing to detect sarcopenia and sarcopenic obesity early, may result in an exacerbated cycle of muscle loss, anabolic resistance and increased risk of comorbidities.

In summary, it is essential that a universally adopted operational protocol is agreed for the classification of obesity, sarcopenia and sarcopenic obesity in older age. It is also suggested that the use of BMI should be complemented with an index of body composition and fat distribution, such as % BF, fat to lean ratio, or lean mass/muscle mass adjusted for BMI, using a practical tool, such as BIA, unless a more robust method such as MRI, DXA or CT is available. As already discussed, BIA can be a very practical and affordable alternative ideal for use at a community level. In addition to body composition, a simple test of strength (e.g. handgrip) or function (walking speed) could be implemented by clinicians and health professionals in clinical settings and research studies for diagnostic purposes, in order to provide a more reliable evaluation of the physical capacity of the individual as recommended by the EWGSOP.

7.2 Recommendations for future research

Firstly, in terms of the operational diagnosis of sarcopenia, obesity and sarcopenic obesity, the sole use of BMI as a classification tool may not be the most appropriate method since the aforementioned conditions can be manifested even with normal BMIs. A large-scale study should

be conducted using either DXA or BIA for the measurement of body composition of older adults, particularly across different areas of Scotland, in order to form a clear picture of the true prevalence rates of sarcopenia and sarcopenic obesity. Dietary intakes should also be assessed in order to draw more robust conclusions about the relationship between protein intakes and body composition/ function. A longitudinal study should be conducted to assess the validity of the different definitions/cut-offs to predict adverse health effects. Secondly, at a community level, since nurses, physicians and GPs are usually the first point of contact for older adults when it comes to health issues, they should be better informed regarding healthy aging strategies and introduce affordable and reliable tests, e.g. walk test or hand grip test alongside BIA, in order to direct older adults to the appropriate health professionals.

Chapter 8. Discussion: A complex exercise and high-protein intervention to augment body composition and function in older age. A randomised controlled trial.

When this study was introduced, it was the first one to combine a nutritional intervention with exercise training for sarcopenic obese older adults. Further, the scope of this study was to be a community-based rather than laboratory based study. Moreover, there is currently a paradigm shift from single ingredients/foods/interventions to more holistic approaches for the treatment of sarcopenic obesity, which underlines the importance and novelty of the current protocol. For example, as discussed later in this chapter, there are emergent studies that utilise the synergistic effect of different concepts such as protein/amino acids ingestion with Vitamin D and/or calcium, alongside exercise training (whole body training with mixed exercise elements). When this study was first designed in 2013, it was one of the first internationally to merge some of these paradigms into one study, targeting sarcopenic obese older adults. Although since then more studies have been published in this area, there is still a substantial lack of interventions providing ≥ 1.2 g protein kg bw^{-1} in older adults (Traylor et al. 2018). In addition, this study is the only one to combine higher protein intakes with a calorie deficit, vitamin D supplementation and whole body mixed exercise training for sarcopenic obese older adults. More importantly, although the sample size was small, this was one of the first studies to show that a substantial amount of fat loss can be achieved with a concomitant preservation of muscle mass. In addition, this is one of the first studies to provide preliminary but targeted evidence on protein intakes of sarcopenic obese older community dwellers.

This chapter discusses the findings of the second part of the thesis, the intervention programme. Only participants who had a low muscle mass index with a concomitant high %BF were eligible to take part in the intervention trial. Changes in body composition, function and blood markers,

along with their dietary intakes are discussed in the following sections. Further, this chapter discusses the applicability of the study protocol to community settings, the challenges faced, and recommendations for future studies.

8.1 Effectiveness of a lifestyle intervention in augmenting body composition and function in older adults with increased body fat and low muscle mass

The challenges faced with sarcopenic obesity are complex considering that the aim of intervention strategies is to attenuate muscle atrophy, while promoting fat loss and a concomitant augmentation of physical function. Relative protein intakes of $> 1.0 \text{ g kg bw}^{-1}$ (and up to 3.0 g kg bw^{-1}) have the potential to suppress muscle mass losses during energy restriction (ER) (Churchward-Venne et al. 2013; Kim et al. 2016b), but in older adults with low muscle and high fat mass the ideal condition would be to attenuate these losses completely. Therefore, the most effective approach for weight loss interventions in obese older adults is to accompany a dietary approach with an exercise programme (Batsis et al. 2017). However, based on the findings presented in *Chapter 2* when this trial was designed there was insufficient evidence of a successful intervention achieving favourable changes in body composition of sarcopenic obese older adults, by exercise, diet or a combined intervention. Therefore, what was achieved in the current study was, and still remains, novel and provides useful information that can inform future studies.

In the present trial an ER diet supplemented by a high-protein drink (resulting in a total daily total of $1.2\text{-}1.5 \text{ g protein kg bw}^{-1}$) led to losses of approximately 5 kg of fat mass, whereas muscle mass was maintained. Participants in the exercise-only group who followed their habitual diet experienced a slightly larger increase in muscle mass of $\sim 0.5 \text{ kg}$ but the change in fat mass was negligible. These results agree with the findings of Batsis et al. (2017), who suggested that exercise

alone can improve physical function but is not likely to lead to significant fat losses. Although these findings need to be confirmed in a bigger cohort, the addition of a protein supplement during ER appears promising in terms of body composition augmentation. However, a clear increase in muscle mass in the protein group was not observed, which could indicate that either a) increasing protein intake may attenuate muscle loss but cannot increase muscle mass more than exercise alone b) protein intake may need to reach > 1.5 g protein kg bw⁻¹ in order to induce hypertrophy, especially in the presence of energy restriction.

Although positive changes in body composition were noted in the current trial with the use of a protein supplement, the effectiveness of protein supplementation in enhancing muscle mass alongside resistance exercise (RE) is controversial (Morton and Phillips 2018). Two recent meta-analyses (Thomas et al. 2016; Morton et al. 2018) supported that the addition of extra protein to a RE regimen may not offer additional benefits in terms of muscle adaptations (size and strength) compared to RE alone, in healthy, frail or sarcopenic older adults. However, the findings of another meta-analysis in older adults (Liao et al. 2017a) were in favour of the synergistic effects of protein supplementation with resistance exercise, while others stand somewhere in between. For example, Finger et al. (2015) reported that protein supplementation with exercise may increase fat free mass but not muscle mass or strength. There are various factors that may account for these discrepant results. First and foremost, the cohorts in the reviewed studies were not homogenous, and as it has been discussed throughout this thesis, the nutritional needs and physiological adaptations can be different in healthy vs obese older adults. Moreover, it is currently unknown whether the anabolic response to protein feeding and exercise is different in older adults who suffer from both sarcopenia and obesity compared to obesity-alone, which therefore, warrants further research. For example, in older sarcopenic obese and non-sarcopenic obese women following exactly the same exercise protocol, only the non-sarcopenic obese group experienced

improvements in body composition (reduced %BF, fat mass and waist circumference) but not the sarcopenic obese group (Silva et al. 2018).

Therefore, the lack of significant change or the discrepancies between studies may also be accounted for by the anabolic resistance phenomenon which can be manifested particularly in obese adults due to a diminished post-prandial MPS in response to protein-dense foods. This was first hypothesised and confirmed by Beals et al. (2016), however, participants in that study were young adults. Recently, Murton et al. (2015) and Smeuninx et al. (2017) confirmed this finding in older individuals. In the study by Smeuninx and colleagues, apart from old age, leg fat mass was found to be significantly negatively associated with myofibrillar protein synthesis in older adults. In addition, in lean older adults the myofibrillar MPS rates rose significantly higher during the post-prandial state (~38%) compared with baseline, whereas in obese older adults MPS did not change significantly (~9%) in either of the groups after ingestion of 15 g milk protein isolate, with both groups having similar muscle mass (Smeuninx et al. 2017). To date, no data exist for the potential differences in MPS rates between sarcopenic obese vs non-sarcopenic obese vs healthy older adults. Therefore, it should be determined whether or not sarcopenia alone or combined with obesity in older age can deteriorate MPS rates, which potentially explains the lack of significant changes in long-term studies with older adults.

Secondly, protein supplementation pre- and/or post exercise training may not offer added benefits in terms of muscle hypertrophy if protein intake is already adequate. It has been shown that supplementation with 20 g protein in older men (76 ± 2 yr) cannot increase muscle fibre size more than exercise alone (~20% increase primarily observed in the type II fibres) (Verdijk et al. 2009). However, the lack of an additive effect might have been accounted for by the fact both groups had similar protein intakes, despite the extra supplemental protein in the intervention group. It has

been often documented in the literature that the addition of extra protein may displace other foods, either by direct replacement of habitual meals or indirectly via enhanced appetite control, e.g. increased feeling of satiation (Ferrando et al. 2010; Arentson-Lantz et al. 2015; Kerstetter et al. 2015). As discussed in Chapter 2, *section 2.4*, this could have influenced the results in the study by Aleman-Mateo et al. (2012), since the addition of cheese to the habitual diet possibly induced faster satiation, and possibly full meals were not completed. Moreover, a high protein breakfast (~ 40 - 50 g protein), may affect appetite hormones (e.g. ghrelin) and impact subsequent meals, leading to reduced appetite and lower energy intake (Pal and Ellis 2010; Jacubowicz et al. 2017). While this would be advantageous for weight-loss purposes, it may add confounders in studies aiming to augment muscle mass in older age. Finally, the composition of the food matrix in the digesta *per se* may affect the rate of appearance of amino acids in circulation, e.g. carbohydrates may delay protein digestion and absorption with no impact on muscle accretion rates in healthy older adults (Gorissen et al. 2014). However, it is unknown whether co-ingestion of nutrients such as carbohydrates, dietary fibres and fat can potentially impact on MPS, positively or negatively, in older adults with reduced anabolic sensitivity.

In the current study, the protein supplement was consumed at times where it theoretically would not directly affect other meals, i.e. immediately after the exercise class, or before bed. The purpose of providing a protein milk in the current study was not to add 50 g of extra protein on top of the habitual diet, but to help participants reach the targets for relative protein intakes ($1.2 - 1.5 \text{ g kg bw}^{-1}$), while restricting moderately their food intakes. Physical activity may affect appetite control and energy intakes, with a single exercise bout reported to increase the perceived pleasantness of high-carbohydrate and high-fat foods in women on restricted diets (Lluch et al. 1998; Beaulieu et al. 2016), which may potentially compromise the ER plan (and possibly even more so in older adults who, as discussed in Chapter 1 *section 1.1.2*, already have a higher preference for ‘sugary’

foods). Therefore, the protein milk administered in this study was advantageous for multiple reasons; potentially greater feelings of satiety that would help participants adhere to the weight loss plan while increasing relative protein intakes, as well as providing a flavoured milk-based protein-carbohydrate load to potentially a) satisfy the need for something sweet after exercise, b) restore glycogen (Biensø et al. 2015), c) rehydrate participants (Shirreffs et al. 2007), especially since dehydration is a widespread issue in older British adults, even in those with higher levels of independence (Wilson 2014), and d) repair and remodel muscle proteins (Phillips and van Loon 2011).

The amount of supplemented protein in studies with middle aged and older adults is only ~20 g, which based on the current knowledge is considered low and may also offer a possible explanation for the lack of added benefits in protein supplementation studies (Morton et al. 2018). As previously discussed, an absolute or relative protein intake per meal should be ~35-40 g or ~0.4-0.5 g kg bw⁻¹, respectively, in order to overcome the anabolic resistance in older adults and significantly increase muscle protein synthesis rates (Moore et al. 2015; Witard et al. 2016b). In a trial with healthy adults aged 50-70 years, increasing relative protein content in breakfast and lunch from ~0.24 g kg bw⁻¹ and 0.31 g kg bw⁻¹, respectively to ≥ 0.4 g kg bw⁻¹, resulted in significant increases in lean mass after 24 weeks (Norton et al. 2016). Further to the relative increase in each meal, the addition of extra protein increased the total relative intakes from 1.2 g kg bw⁻¹ to 1.6 g kg bw⁻¹. Therefore, when the addition of protein increases total and relative protein intakes, it has the potential to improve body composition. However, these findings were during energy balance, and not under conditions of ER.

In the current study, a protein intake of a similar range was effective in maintaining muscle mass but not increasing it. Therefore, it could be hypothesised that during ER, protein intakes > 1.6g kg

bw^{-1} are needed to elicit muscle hypertrophy in older adults, especially since ER can lead to a higher utilization of amino acids for energy production and make less available for tissue synthesis (Stokes et al. 2018). For example, during a 40% ER in younger adults, protein intakes of 1.6-2.4 g kg bw^{-1} sustained MPS to rates comparable with those under energy balance (Pasiakos et al. 2013). However, even if anabolic sensitivity is sustained, the absence of exercise is a limiting factor, which can eventually lead to muscle losses after three weeks of ER when protein intakes are reported to be 0.8 g kg bw^{-1} , 1.6 g kg bw^{-1} , or even as high as 2.4 g kg bw^{-1} (Pasiakos et al. 2013). Thus, it is not surprising that an ER diet providing 1.2 g kg bw^{-1} did not manage to attenuate muscle loss in the absence of exercise in postmenopausal women (Smith et al. 2018). Even higher relative intakes, ~ 1.7 g kg bw^{-1} failed to maintain muscle mass in older overweight adults during a 25% ER diet (1.8 ± 2.2 kg lean body mass was lost over 12 weeks) (Backx et al. 2016). On the other hand, the addition of resistance exercise to an ER diet providing 1.3 g kg bw^{-1} protein was able to elevate myofibrillar MPS by $\sim 26\%$ in overweight and obese older adults, and maintain appendicular muscle mass [change of 0.0 ± 0.7 kg] within a period of two weeks (Murphy et al. 2015; Murphy et al. 2018). In fact, the elevation in MPS was independent of the feeding pattern, that is, MPS was similar between balanced feeding (four meals containing 25% of the daily protein needs) vs a skewed pattern (72% of daily protein supplied in dinner). Nevertheless, these findings should be interpreted with caution since results from acute/short term studies may not always agree with long-term studies and/or in groups with different characteristics. For example, in a six-week study by Boullanne et al. (2013) involving 66 older, malnourished (or at risk of malnutrition) rehabilitation patients ($\text{BMI} \leq 22$ kg m^{-2}), a skewed distribution ($\sim 70\%$ of the protein consumed in the midday meal), resulted in significantly higher skeletal muscle mass index ($+0.2$ kg m^{-2} vs -0.1 kg m^{-2} in the balanced group), even though the total relative intake in both groups was the same (1.3 g kg bw^{-1}). These discrepancies may be as a result of the ‘skewed-pattern’ diet providing at least one meal with $> 30\text{-}40$ g protein (vs ≤ 20 g in all meals in the balanced diet), whereas in the

study by Murphy et al. (2018) all meals in the balanced diet contained ≥ 30 g protein accompanied by resistance exercise, which most likely enhanced the anabolic response in both groups. These findings are in agreement with the current study, highlighting that as long as there is one meal with enough protein to optimally stimulate MPS in the presence of exercise training, then muscle mass can be maintained during ER-induced weight loss, independent of the feeding pattern.

In younger adults who followed an ER diet only, protein intakes of ~ 2.4 g kg bw⁻¹ accompanied by resistance exercise training can acutely elevate MPS to a degree that can eventually not only maintain lean mass but also increase lean mass while reducing fat mass across four weeks (Longland et al. 2016; Hector et al. 2018). Energy restriction can reduce MPS, and a lower MPS is believed to be the culprit of reduced muscle mass during ER. Therefore, providing ample protein is crucial, though the effectiveness of such high protein ranges has yet to be demonstrated in older adults. On the other hand, it is pivotal to acknowledge that perhaps no practical upper limit for protein intake that can maximise net protein balance exists (Deutz and Wolfe 2013). However, it can also be speculated that providing a very high amount of protein to the extent that it can suppress muscle breakdown and interfere with muscle remodelling (i.e. autophagy) would not be advantageous (Stokes et al. 2018). As previously discussed, impaired autophagy (diminished ability to restructure protein tissue) is associated with reduced muscle quality and quantity, and consequently, with frailty and sarcopenia (López-Otín et al. 2013). However, whether dietary manipulations can lead to impaired autophagy in older adults, and if so to what extent, is unknown.

Since the completion of the systematic review, several new studies have been published with sarcopenic obese adults participating in exercise (Vasconcelos et al. 2016; Chen et al. 2017; Cunha et al. 2017; Huang et al. 2017; Liao et al. 2017b; Silva et al. 2018), nutritional (Muscariello et al. 2016; Sammarco et al. 2017;), or combined interventions (Kim et al. 2016a), however, the ranges

of relative protein intakes provided were not higher than the ones employed by the current study. Muscariello et al. (2016) and Sammarco et al. (2017) are the only recent studies that employed a weight loss diet in sarcopenic obese adults. Similar to the current protocol, they combined ER with protein intakes of 1.2 g kg bw⁻¹ (Muscariello et al. 2016) and 1.2 – 1.4 g kg bw⁻¹ (Sammarco et al. 2017). In the study by Sammarco and colleagues the energy deficit was 500-600 kcal, over four months. However, protein intakes of the control group were not reported, there was no exercise protocol, and the population cohort was not homogenous (n=19 women, age 52 ± 8 yr; age range: 41-71 yr). Nevertheless, fat loss was similar to that reported in the present study (~5 kg; from 51.3± 10.9 kg to 46.3± 12.3 kg) and proportionally more than the one reported by Muscariello et al. (2016) (~2.4 kg from 34.2± 4.3 to 31.8± 1.2 kg; n=108), which had a shorter period (three months) and possibly a smaller energy deficit. The diet provided 20-25 kcal kg⁻¹ desirable bodyweight but it was not elaborated how desirable bodyweight was calculated. In relative agreement with the current results, skeletal muscle index increased in the study by Muscariello et al. (2016) in participants who performed 30 min of physical activities for at least five days week⁻¹ (no structured classes or other equipment/protocols were provided). Muscle mass index increased significantly in the high protein group (from 6.9± 0.1 kg m⁻² to 7.1± 0.4 kg m⁻²), whereas declined significantly in the normal protein group (0.8 g kg bw⁻¹) from (7.1± 0.2 kg m⁻² to 6.9± 0.1 kg m⁻²), which is comparable to the change noted in the current study in EXD group (*section 6.4*). In the study by Sammarco et al. (2017), although participants followed their habitual lifestyle (no information on physical activities provided) an increase in fat free mass was noted (from 47.6 ± 2.5 kg to 48.7± 2.1 kg), however, changes in muscle mass or muscle index were not provided, and therefore, increases in fat free mass may have been as a result of increases in muscle as well as connective tissue (Bosy-Westphal and Müller 2015).

The approximate loss of ~5 kg in fat mass observed in the current study and in the study by Sammarco et al. (2017) over a 4-month period was proportionally higher compared to the loss of ~2.4 kg over three months reported by Muscariello et al. (2016). This difference may be accounted for by the energy deficit, which in the current study and that of Sammarco et al. (2017) was 500 kcal, compared to an approximate estimate of ~300-500 kcal deficit employed by Muscariello and colleagues. It would have been interesting to compare compliance rates to dietary plans between studies, however, compliance was only reported in the current study. Moreover, the exercise protocol in the current study, albeit not of a high intensity, ensured that all participants engaged with mixed exercise training, which could potentially increase total energy expenditure and therefore, promote more fat loss. Additionally, median protein intake in the current study was 1.4 g kg bw⁻¹, which is higher than the 1.2 g kg bw⁻¹ adopted by Muscariello et al. (2016), and was not reported by Sammarco et al. (2017), although authors aimed for similar protein intakes. Protein intakes may account for differences not only in muscle but also fat mass, since older adults undertaking an energy deficit diet are likely to lose more fat mass and retain more lean mass during the active weight loss period when consuming higher amounts of protein (Kim et al. 2016b). Sammarco et al. (2017) also noted an increase in fat free mass with a concomitant reduction in fat mass, which was surprising given the ER regimen and the absence of exercise training. However, this could be attributed to the fact that participants were younger, and perhaps more receptive to the anabolic stimuli of protein feeding and/or increased their physical activity levels (which were not measured).

In order to interpret the findings of the current study and compare them with similar weight loss studies, the fundamental element to consider is energy deficit. Although as a generic rule, 3,500 kcal deficit is required to produce 0.45 kg (1 lb) of fat loss (originally introduced by Wishnofsky 1952), the magnitude of this deficit-associated weight loss is likely to decline markedly over time

(Heymsfield et al. 2012). Metabolic adaptations resulting from loss of energetically active tissue such as muscle, and the reduced caloric expenditure associated with weight-bearing movements, are principally responsible for this non-linear decrease in weight (Heymsfield et al. 2012). Moreover, other parameters, such as initial body weight and body composition may further confound weight loss, with obese individuals perhaps requiring a greater deficit than their eutrophic counterparts for any given amount of weight lost. Therefore, it was proposed that intentional weight loss does not come at a fixed value of 3,500 kcal lb⁻¹ (or 3,500 kcal per 0.45 kg) but is a dynamic process that can fluctuate for several weeks, and more importantly can also differ between men and women (Heymsfield et al. 2012). This theory agrees with Muller et al. (2016) who suggested that there are inter-individual differences in weight loss paradigms due to several factors, such as energy intake, diet composition, baseline fat mass and muscle mass, activity levels, the metabolic state of the individual and hormonal responses to dietary changes. Moreover, although gene expression profiles related to weight loss are activated linearly with the magnitude of ER, it has been recently suggested that there are pathways that do not follow that rule and may ‘switch on’ at certain thresholds, thus, may be activated at 40% ER, but not at 20% or 30% (Derous et al. 2017). Therefore, the effect of ER on genetic transcription can be a confounder. Although the current study has estimated the expected losses over a certain period of time based on the 3,500 kcal lb⁻¹ rule (in the present study 0.45 kg or 1 lb week⁻¹), realistically speaking the resultant weight loss is likely to be lower, considering also that adherence to diet cannot be 100%. Nevertheless, the important finding of all three studies in sarcopenic obese adults was that an increased protein intake (1.2-1.5 g kg bw⁻¹) alongside a moderate energy deficit can result in a rate of fat loss ~0.8 - 1.2 kg month⁻¹ while preserving muscle tissue.

It can be hypothesised that the changes in body composition noted in the intervention arm of the current study, and primarily the loss of body fat, were accounted for by the dietary aspect of the

protocol, i.e. the energy deficit and increased protein intakes, and not because of the addition of vitamin D. This hypothesis is in agreement with a trial that included postmenopausal obese (but not sarcopenic obese) adults ($n=24$), consuming $1.2 - 1.5$ g protein kg bw^{-1} alongside a daily deficit of ~ 400 kcal (Gordon et al. 2008). The intervention resulted in fat mass losses of 6.3 ± 3.0 kg fat mass after six months (≈ 1.05 kg of fat loss per month). Although this figure is proportionally slightly lower than the current one, the small discrepancy may be accounted for by the increased deficit employed in the current study combined with the exercise regimen. In a study by Gordon et al. (2008), all participants were supplemented with $25 \mu\text{g}$ vitamin D daily to ensure adequate serum 25 (OH) D concentrations. Although a mean loss of 17% in lean mass was reported, changes in muscle mass were not measured, which would have provided a direct comparison between the two studies in order to examine the effect of the exercise and nutritional regimen on muscle mass. Although the studies are not conclusive, it seems that the addition of vitamin D to a weight loss high-protein diet does not further augment body composition, which also agrees with the findings of a meta-analysis of trials in older adults undergoing an exercise training routine with supplemental Vitamin D (Antoniak and Greig 2017).

Apart from dietary modifications, exercise is a key factor for potentially favourable physiological adaptations. In this study a multi-component moderate-intensity exercise regimen was employed, with aerobic, balance, resistance, and flexibility elements. The exercise-only group of the current study experienced small numerical improvements in body composition, and although not known if statistically significant, an important outcome was the attenuation of muscle loss. Changes of ~ 1 kg in muscle mass in four to six months exercise interventions with older adults can be expected, and regardless of statistical significance they can be of clinical importance considering that without exercise the annual expected loss is ~ 0.2 kg in muscle mass (Peterson et al. 2011) which may be possibly greater in sarcopenic obesity. Although similar protocols have been found

effective for reducing the risk of falls and physical disability in older adults (Baker et al. 2007), there are only a few exercise studies targeting specifically at sarcopenic obese adults in the literature. Chen et al. (2017) assessed the effect of different types of exercise training on body composition and strength in 60 Japanese sarcopenic obese participants, aged 65 – 75 years. The study consisted of a resistance-only, aerobic-only, combined group (resistance and aerobic), and a control group exercise twice weekly for 12 weeks. The resistance group performed 8-12 repetitions for three sets at 60%-70% 1RM. The aerobic group performed 5-10 min of stretching followed by aerobic exercises such as dance steps, leg and arm swings, combination steps (e.g. diamond steps, mumbo steps etc.) followed by 10 min of relaxing exercises. The combined group, alternated between an aerobic and a resistance session, whereas the control group followed their habitual lifestyle. Skeletal muscle mass increased similarly (approximately +0.2 kg) in all exercise groups whereas it decreased on average by 0.7 kg in the control group. At the end of the trial, marginal increases in muscle mass led to significantly greater SMM for all three exercise groups compared with the control group. The changes in the exercise groups are in agreement with the changes observed in the current study, not only in the exercise-only group but also in the exercise and diet group. Therefore, a change as low as +0.1 kg in muscle mass during caloric restriction should not be undervalued since it is on par with changes in studies without energy deficit, and additionally, it is unequivocally better than losses in muscle mass.

It appears that changes of ± 1 kg of muscle and fat mass are expected in studies with sarcopenic obese older adults after 12 weeks of resistance exercise training (Cunha et al. 2017; Huang et al. 2017; Liao et al. 2017b). For example, Huang et al. (2017) and Cunha et al. (2017) used a progressive resistance training programme for sarcopenic obese older adults with elastic bands (three weekly sessions, three sets x 10 reps at a moderate-high intensity of ~13 RPE Borg) which were similar to the current study. The changes noted were in the range of -1.0 kg to 0.3 kg for

muscle mass and -0.6 kg to -0.7 kg for fat mass. In contrast with these findings, Vasconcelos et al. (2016) and Silva et al. (2018) found no changes in the body composition of sarcopenic obese adults after a 10-week and 16-week RE trial, respectively. The study by Vasconcelos et al. (2016) employed a similar protocol to that of Balachandran et al. (2014) (discussed in detail in Chapter 2), with the concentric part of the exercises performed as fast as possible, with both studies reporting no effect on body composition. Apart from the velocity of performed movements, the difference between these two studies and those that observed improvements in body composition was that the exercise sessions were twice a week and not three times. As discussed previously, frequency and volume are important factors, which has also been recently demonstrated by Cunha et al. (2017), who showed that an increased number of sets (three sets vs one set per exercise) performed three times weekly by sarcopenic obese older adults can significantly improve their muscle mass by ~1 kg, while reducing % body fat by ~2%. Despite the lack of body composition changes in the sarcopenic obese group (Silva et al. 2018), the important finding was that the healthy control group who followed the same exact exercise programme as the sarcopenic obese group, noted a significant improvement in body fat, waist circumference and waist to hip ratio. The sarcopenic obese phenotype was identified based on low FFMI and a BMI $\geq 27 \text{ kg m}^{-2}$ which underlines again that impaired physiological adaptations in older age may come at BMIs lower than 30 kg m^{-2} .

The only other study to date examining the combined effects of a nutritional intervention with exercise training on body composition and function in sarcopenic obesity reported non-significant changes in fat mass (~ -0.7 kg) and muscle mass (~ +0.2 kg) (Kim et al. 2016a). The nutritional plan involved the daily administration of a leucine-rich supplement (1.2 g leucine complemented with all EAAs for a total quantity of 3 g), a vitamin D3 supplement ($20 \mu\text{g day}^{-1}$) and tea rich in

catechins (540 mg) for three months, without energy restriction. The exercise programme was similar to the current study, however took place only twice a week. No significant time x group interactions were noted (four groups: nutrition-only, exercise only, exercise + nutrition, health education) in absolute fat mass, muscle mass or grip strength, therefore it could be suggested that Vitamin D supplementation (even alongside a small dose of leucine and EAAs) cannot amplify the effects of exercise training. Therefore, it could be proposed that exercise alone can attenuate muscle loss in the absence of energy restriction, potentially alongside some small losses of fat mass in sarcopenic obese older adults, even in the absence of protein/vitamin D supplementation.

Regarding strength and function, grip strength was numerically improved in the current study, possibly because upper body was engaged (although in low intensity exercises) in every session, adding to the total exercise volume and frequency of muscle engaged. As Schoenfeld and colleagues have demonstrated in recent meta-analyses, there is a graded dose-response relationship between number of sets and muscle growth, and additionally, major muscle groups should be engaged at least twice a week for muscle hypertrophy purposes (Schoenfeld et al. 2016; Schoenfeld et al. 2017). This agrees with Borde et al. (2015), who proposed that training frequency is pivotal (\geq twice weekly), as is volume (2-3 sets, \sim 10 repetitions per exercise) and time under tension (\sim 6 s per repetition) for both muscle strength and morphology (e.g. size of type II fibres) to improve. However time under tension in the current study was only \sim 2 s in the first 14 weeks and 3 s (1 s for the concentric and 2 s for the eccentric) in the last two, which may explain to some degree the lack of substantial improvements in muscle mass.

Therefore, based on the latter findings, the lack of changes in handgrip strength in the resistance and aerobic exercise group by Chen et al. (2017) may be accounted for by the low volume and frequency of exercise training for the upper body (only once a week), whereas lower body muscles

were engaged twice a week (both during resistance-only and aerobic-only). As an outcome, knee and back extensor muscle strength were reported to be significantly higher in the resistance-only and in the combined-exercise group when compared to the control group after 12 weeks of exercise training. In the grip-strength test the resistance-only group scored significantly higher compared with the other groups, and was the only group with improved strength (+2.1 kg) over time. It is important to note that hand-grip was increased by 3.5 kg by week-8 in the resistance-only group but the improvement at week-12 was finally 2.1 kg. This improvement is in accordance with the changes observed in the current study (~ 2.0 kg) and Kwon et al. (2015b). However, as Nitschke et al. (1999) have shown, day-to-day variations in hand grip may fluctuate by as much as ~6 kg. Therefore, it is suggested that in order to confirm strong improvements in hand grip, the changes must exceed this threshold of +6 kg.

The previous finding also agrees with a study by Kim et al. (2014), who proposed a minimal clinically significant difference of ~6.5 kg or a change of 20% in hand grip strength. However, this should be interpreted with caution as the study was conducted in young, middle aged, and older women during rehabilitation from a distal radius fracture. Scientists have used the concepts of meaningful (or clinically significant) change to evaluate the effectiveness of treatments and whether a change noted is clinically important for the health status of the individual, regardless of statistical differences. Such values are the ‘minimal clinically important differences’ (MCID) and ‘minimal detectable changes’ (MDCs). However even the MDCs and MCIDs depends on the population characteristics, the standard deviation, intra-class correlation coefficient (ICC), standard error of the mean (SEM) or the validity of the independent test that has been used as an ‘anchor’ (Chui et al. 2012). For example, in middle aged and older patients with hand osteoarthritis the MCID for hand grip may be 0.8 kg and 1.1 kg for the affected and the unaffected body side, respectively. In the only other study with a weight loss regimen and higher protein intakes, hand

grip did not change significantly (neither statistically nor clinically), indicating that perhaps exercise training is the main driving factor of changes in strength, regardless of protein intake (Muscariello et al. 2016).

In terms of physical function, in the current study both groups noted improvements in gait speed, but EXD experienced a more pronounced improvement by 0.4 m s^{-1} . In the study by Kim et al. (2016a) no significant changes were identified in grip strength (-0.2 kg in the exercise-only group to $+0.5 \text{ kg}$ in nutrition and exercise group) either between or within groups or over time. However, a significant time x group interaction was noted for walking speed which increased by $\sim 0.2 \text{ m s}^{-1}$ in the exercise only group and by $\sim 0.1 \text{ m s}^{-1}$ in the other groups. These improvements are in accordance with those noted in the current study, and in the absence of significant increases in muscle mass, they may be accounted for mainly by neuromuscular adaptations, which usually tend to occur over the first 10 weeks of exercise training (Steib et al. 2010). Nevertheless, even an improvement of $+0.05 \text{ m s}^{-1}$ can indicate a small meaningful change in gait speed in older community-dwellers, with a change of $+0.1 \text{ m s}^{-1}$ indicating a substantial change for community-dwellers as well as individuals with comorbidities such as Parkinson's disease, stroke, Alzheimer's disease, and patients with hip fractures and osteoarthritis (Perera et al. 2006; Chui et al. 2012). Moreover, an increase of 0.1 m s^{-1} can be predictive of better survival in older adults, indicating a substantial improvement especially in the exercise-only group of the current study. Further, this shows that changes in function may be closely related to handgrip strength, however, substantial changes in strength are not a prerequisite for improvements in function.

Indeed, although absolute changes in strength are important, studies have also suggested that maximal strength gains are not essential for functional improvements (Orr et al. 2006; Steib et al. 2010). In fact, power training (i.e. force generation at high velocities) can effectively improve

muscle power and functionality in older adults (Steib et al. 2010). Two tests reflecting changes in functional improvement and especially leg power in the current study were the timed up and go (TUG) test and repeated chair stands; in which functional improvements were noted in both groups (with EX experiencing greater numerical improvement; *section 6.5*), which surpassed the cut-off of 1.7 s for a minimal difference of clinical importance (Jones et al. 2013).

The findings of the current study highlight the importance of exercise training, even at moderate intensities, and regardless of dietary changes and weight loss. A recent systematic review by Byrne et al. (2016) has detailed the importance of muscle power and functionality in older age and how these outcomes can improve across a range of different exercise intensities, in the absence of dietary modifications. In fact, increased power and physical function can occur even at low-moderate intensities, that is, 20% - 40% 1RM (Orr et al. 2006; Reid et al. 2015). Orr et al. (2006) demonstrated that older men and women exercising twice a week for 8-12 weeks at intensities 20% 1RM at a fast concentric/slow eccentric fashion (a similar pattern was employed towards the end of the current trial), can experience significant improvements in balance. Similarly, Reid et al. (2015) demonstrated that exercising at 40% 1RM can significantly increase SPPB results by ~1.3 points, which was not statistically different to the increase noted in their high intensity group (70% 1RM). This demonstrates that exercising at low-moderate intensities can improve physical function. Although in the current study SPPB scores were considerably high at baseline, numerical improvements were still seen that can be of clinical importance (*section 6.5*). Namely, changes of +0.5 and +1.0 in SPPB may indicate small but meaningful changes, and substantial changes respectively (Perera et al. 2006). Even an attenuation of the decline in SPPB (and its individual domains) may be important since score decreases of ≥ 1 points may increase subsequent five year mortality rates (Perera et al. 2005).

The above findings are in accordance with a meta-analysis by Steib et al. (2010) highlighting that significant improvements in functional tasks such as the ones performed in the present study e.g. timed up-and-go (TUG) test, repeated chair rise and gait speed, can be anticipated after a resistance exercise programme, with the magnitude of adaptations independent of exercise intensity. This phenomenon may be accounted for by several reasons. For example, sedentary and especially older adults with low to moderate strength may respond well to exercise training even at low training stimuli, which may be explained by the enhanced neuromuscular coordination, as mentioned previously (Steib et al. 2010). Moreover, a certain strength threshold exists, above which changes in strength do not necessarily translate into proportional changes in function (i.e. a 20% increase in strength does not indicate a 20% increase in gait speed). This has been long established by Buchner et al. (1996), who suggested that strength training in older adults with low to moderate strength can have a substantial effect on physical performance, however, after a certain point any further gains in strength may benefit the physiological reserves but not function *per se*.

Dynamic balance as assessed by 1-arm functional reach, presented numerical improvements with a noticeably greater absolute increase in the EX group (~8 cm) (*section 6.5*). It is established that simple progressive resistance exercise programmes utilizing elastic bands can improve functional reach by ~4 cm (McMurdo and Johnstone 1995), and this improvement is independent of lower-limb strength gains (Chandler et al. 1998). Ramsbottom et al. (2004) have reported significant improvements in functional reach, in an exercise programme comparable to the current one. Healthy older adults took part in two exercise classes weekly for 24 weeks. Single-arm reach test significantly increased from 23 cm to 34 cm in the exercise group, which was similar to the increase noted in the current study. Based on an analysis of four studies with older adults (community-dwellers, care-home residents, with Parkinson's disease, or after hip fracture) a

meaningful change in 1-arm reach test has been reported to range from 4-11 cm (Steffen and Seney 2008), which indicates that the exercise-only group in the current study experienced a clinically significant improvement. It is surprising, however, the fact that the EXD group did not note a similar change. It could be speculated that the EXD group had already scored well at baseline, and due to the nature of the test itself, there is only a certain amount of change that is physiologically/biomechanically feasible. Perhaps individual differences, such as height and limb length may also limit the amount of improvement that can be achieved in this test.

The results noted in the current study for the TUG test were comparable at baseline with those of Ramsbottom et al. (2004), with groups reporting times of ~7 s, to complete a full course. In the present study however, the improvement was noticeable with a decrease of ~2 s in both groups. Ramsbottom and colleagues showed that a decrease in time to complete TUG by ~1 s can indicate a statistically significant improvement, which is also close to the MDC value (1.1 – 1.4 s) (Wright et al. 2011; Alghadir et al. 2015). Although the decrease in fat mass experienced by the intervention group in the current study should theoretically have provided these subjects with an extra advantage compared to the control group, the improvements in TUG test were numerically similar in both groups, suggesting that exercise training may improve function independent of a diet-induced weight loss.

Although the statistical significance should be corroborated statistically, it is suggested that the exercise training alone accounts for most of the functional improvements noted in the present study. For these numerical –and some clinically substantial- improvements, apart from the resistance generated by bodyweight exercises and the resistance bands, there were additional techniques that were employed and could account for the increased power and subsequent functional improvements. For example, during balance and aerobic training, exercises requiring

change of direction or swift step sequences were employed. Weight bearing exercises, such as chair stands (or squats with elastic bands) and press-ups against the wall, were performed at higher velocities, once participants started to feel more confident and able to move faster. Moreover, the band exercises during the last two weeks of the training were performed at maximum voluntary velocity. As discussed earlier, muscle retains its plasticity and ability to adapt to external stimuli even in old age. Therefore, exercising at low intensities has the potential to augment physical function, while offering the extra advantage of a lower perceived effort (Reid et al. 2015), which is pivotal in older age (Byrne et al. 2016). Perhaps tests requiring participants to move their body over a longer distance, e.g. the 400 m walk test and time-trials or repeated chair stands for 60 s, would have shown greater improvements in physical function in the EXD group since a large amount of fat mass was lost, and this should theoretically improve tasks that require body mass to be moved over space or for prolonged periods of time.

In relation to quality of life, although a statistical significance was not confirmed in the present study, it is a positive outcome that numerical improvements were noted in most domains, and especially the ones regarding general health and perceived health in comparison with the previous year. The fact that the baseline scores for many of the HRQoL were already high indicates that the results might have suffered from the ceiling effect. That is, independent-living community dwellers who have the physical, mental and emotional capacity to take part in research studies, including exercise classes and dietary changes, are likely to be above average in terms of HRQoL compared with their counterparts and therefore, substantial subsequent changes in HRQoL domains are unlikely (de Vreede et al. 2007; Kwon et al. 2015b). Indeed, data from the Scottish Health Survey have indicated that the majority of adults ≥ 65 years in Scotland (41.2%) have scored in the lowest quintile for physical function (lowest quintile: < 42 points; $n=435$), whereas only 7.3% ($n=76$) scored in the highest quintile (> 56 points) (Ul-Haq et al. 2014). The higher

scores in HRQoL noted in the current study may therefore, reflect positive attitudes towards changes that may improve health (Ul-Haq et al. 2014), a theory that parallels with the willingness of participants to commit to the current four month research trial. None of the domains that scored ≤ 70 at baseline decreased at the end of the trial, indicating that the numerical decreases were seen only in those domains with very high scores at baseline (≥ 80). This has also been observed in another study with sarcopenic obese participants, who after 10 weeks of exercise training did not report any significant improvements either over time or compared to the control group (no exercise), possibly because QoL scores were already high at baseline (≥ 80) (Vasconcelos et al. 2018). An anecdotal observation of the current study was that before, during or after the exercise classes, participants would frequently express concerns about the health status of people closely related to them, such as family members and friends. Such concerns seemed to have a negative effect on their mood, psychological status, and overall motivation. Perhaps this may account for the numerical decrease in emotional well-being in EXD, however, given that the group size was small, relatively trivial changes had the potential to skew the overall results, thus is important to interpret these results with caution.

It could be speculated that the use of elastic bands lacks the element of a quantifiable progression in numerical terms. For example, one may find it easier to follow the progress made on resistance machines with a fixed and measurable resistance. Although participants were satisfied when they could advance one colour in the elastic band progression scale, the increase in their strength was not something that could be easily gauged. This is in agreement with Damush and Damush (1999) who noted that despite a resistance exercise programme for older women who exercised with elastic bands, was very practical, inexpensive and produced significant improvements in strength and function, in terms of perceived changes in quality of life domains, it may actually offer little benefits. This has also been proposed by Kwon et al. (2015b) who assessed changes in function

and QoL in 89 older adults with low muscle mass and strength after three months of training with elastic bands with/without participation in nutrition education classes. Although a mean change of +2.3 kg in handgrip strength was deemed significant in the exercise-only group, there were no subsequent changes observed in HRQoL domains; whereas the group that undertook exercise and cooking classes experienced a significant improvement in QoL domains, such as role limitations due to physical and emotional health, and bodily pain. Therefore, it is possible that despite the physical improvements from the exercise programme, the social interaction aspect was possibly the key parameter in improving perceived quality of life, with participants spending a few hours each week participating in shopping, cooking and eating together, something that enhanced the communication and relationship-building aspect of the programme. Moreover, Kwon et al. (2015b) suggested that bodily pain is likely to progress with ageing and it may not change or improve within a short period of time in older adults. Even in studies of ≥ 12 months duration, progression of pain has been reported (Sato et al. 2009).

From analysing the Scottish Health Survey data, the physical function domain seems to be one of the most important predictors of overall mortality and coronary heart disease events (Ul-Haq et al. 2014). In the present study, even though the physical function domain scored high at baseline, it still improved by 5-10 points in both study groups. Even such numerically small changes may be important since a decrease of 5-10 points in physical domain is associated with higher risk of mortality in older adults (Tsai et al. 2007; Otero-Rodriguez et al. 2010). The analysis of HRQoL in Scottish adults also showed that the physical function domain can predict mortality independent of adiposity, when the latter is defined as high BMI. This finding agrees with the overall concept of the current research, proposing that it is the relative contribution of muscle mass/function and adiposity that should be utilised instead of BMI, since for any given category of BMI the body composition phenotypes of individuals can differ considerably.

8.2 Dietary intake

The current study is one of the first to present dietary patterns in older adults with low muscle mass and high body fat. The analysis of dietary intakes showed that participants followed a diet with a nutritional composition similar to the national average, with two exceptions. Energy intake was higher in the current cohort of women vs the national average, whereas relative energy contribution from protein was lower (*section 6.2*). It can be suggested that the current cohort were consuming more energy for proportionally less protein compared to the population average. The protein intake relative to bodyweight was $0.9 \text{ g kg bw}^{-1} \text{ day}^{-1}$, and since there are no NDNS data on this, a direct comparison cannot be made. In addition, a skewed pattern of protein intakes with low amounts of protein consumed at breakfast ($\sim 10 \text{ g}$) and a proportional rise in protein at subsequent meals ($\sim 20 \text{ g}$ and $\sim 30 \text{ g}$ in lunch and dinner, respectively) was noted (*section 6.2*). It is important to note that these data refer to habitual intakes at baseline, before the introduction of any supplements or dietary modifications.

These findings also highlight the fact that although several studies and specialist committees on healthy ageing have advocated the importance of increasing protein intake from $0.8 \text{ g} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$ to $1.2 - 1.5 \text{ g} \cdot \text{kg bw}^{-1} \cdot \text{day}^{-1}$ (Wolfe 2012; Deutz et al. 2014) it is questionable whether such practices have been adopted by all population groups, and in particular by those in most need. It is also pivotal to consider the fact that, even with protein intakes adhering to the current recommendations ($\sim 0.8 \text{ g kg bw}^{-1} \text{ day}^{-1}$), older adults can be in negative nitrogen balance during periods of physical inactivity (Ferrando et al. 2010), and increased protein intakes alone cannot attenuate the inactivity-induced loss of muscle mass (Ferrando et al 2010; Dirks et al. 2017). Therefore, focusing only on absolute intakes of protein without taking into consideration other

important parameters such as physical activity, and total energy intakes may not allow for a complete appreciation of the magnitude of this relationship.

Perhaps the only recent UK dataset that can be compared with the current study is that by Cardon-Thomas et al. (2017). In an observational study with 38 ambulatory and free-living community dwellers (n=27 women; n=11 men, aged ≥ 70 years, 68 ± 12 kg), mean energy intake was 1815 ± 363 kcal, however, 30% of participants were men, which probably influenced mean energy intake. Mean protein intake was 1.14 ± 0.25 g kg bw⁻¹, and protein contributed to energy intake by 17 ± 3.4 % (Cardon-Thomas et al. 2017). It is noteworthy that 92% and 76% of the cohort consumed more than 0.8 g kg bw⁻¹ day⁻¹ and 1.0 g kg bw⁻¹ day⁻¹, respectively in the aforementioned study. These figures are higher compared with those reported in the current study. Given that body composition was not measured by Cardon-Thomas et al. (2017), whereas in the present study all participants had low muscle and high fat mass, it could be suggested that the low protein intakes reported in the current study may account to some extent for the low muscle mass and high % BF of participants. In the study by Cardon-Thomas et al. (2017) the daily protein distribution was skewed, with breakfast, lunch and dinner providing 18%, 39% and 44% of the daily protein intake, a pattern that is consistent with the findings of the current study. Therefore, it can be hypothesised that it is not the skewed pattern that affects body composition, instead it may be the total relative protein intakes. Indeed, as Houston et al. (2017) have proposed, those consuming < 1.0 g kg bw⁻¹ day⁻¹ (and particularly those consuming ≤ 0.7 g kg bw⁻¹ day⁻¹) may be at increased risk of sarcopenia compared to those consuming ≥ 1.0 g kg bw⁻¹ day⁻¹. Therefore it could be proposed that in the normal distribution curve of protein intakes for the overall older population, the sarcopenic obese subgroup may lie at the lower end.

The previous hypothesis may also explain the higher (numerically) absolute relative intakes reported in healthy older subgroups (Cardon-Thomas et al. 2017) or the general 65+ UK population (Millward 2012) compared with the intakes from the present study, which however, noted a similar or even higher energy intake. Nevertheless, since there is a lack of comparative studies that investigate muscle mass/function with different protein intakes, in older (and especially sarcopenic obese) Scottish adults, unequivocal conclusions cannot be drawn. Without larger and long-term studies it is also not clear whether low protein intakes are an independent risk factor for sarcopenic obesity, or that low protein intakes are the outcome of a combination of inactive lifestyles, anorexia of ageing, cognitive or psycho-social factors, inflammation, and other factors that may also lead to sarcopenia and obesity (Millward 2012). The latter agrees with Cardon-Thomas et al. (2017) who noted that protein intake was significantly and positively correlated with step count but inversely correlated with age and sedentary time; therefore, it can be hypothesised that those who were younger and more physically active reported higher relative protein intakes. Another important parameter is socioeconomic status which can influence protein intakes and therefore, should be considered in observational studies (Beasley et al. 2010). However, such information was not collected in the current study, which reflects a limitation.

One of the largest European studies that has provided valuable information regarding dietary intakes and distribution of protein consumption is that by Tieland et al. (2012b), who assessed habitual intakes of 707 community-dwellers, 194 frail, and 286 institutionalised Dutch older adults (BMIs ~ 23 - 27 kg m⁻²). The institutionalized group consumed significantly less protein compared to the frail group and the free-living community dwellers (~0.8 g kg bw⁻¹ vs ~1.0 g kg bw⁻¹ vs ~1.1 g kg bw⁻¹, respectively). Their findings are consistent with the current study and those by Cardon-Thomas et al. (2017), noting skewed protein distributions across the day; intakes gradually increased from breakfast (8 g in frail, 10 g in institutionalized and 12 g in community dwellers) to

lunch (18 g in frail, 25 g in institutionalized and 29 g in community-dwellers) and dinner (15g in institutionalized, 29 in frail and 30 g in community-dwellers). Therefore, this skewed pattern possibly characterizes the majority of the older populations in Europe (healthy independent living, frail, institutionalised etc.) and not just those in the UK who are sarcopenic obese, thus it would not be prudent to assume that the skewed distribution *per se* is the driving factor for frailty or sarcopenic obesity.

In another large European study (n=900 adults, ≥ 60 years from the Nordic countries), it was shown that only ~25% of the entire cohort reached targets $> 1.2 \text{ g kg bw}^{-1} \text{ day}^{-1}$, and this was primarily due to a large cohort of participants taking part in cooking classes (Jyvakorpi et al. 2015). Therefore, it can be suggested that knowledge of healthy eating can be important. Moreover, although mean daily protein intake of the overall population was approximately 1.0 g kg bw^{-1} , around one third of the whole population cohort did not achieve the 0.8 g kg bw^{-1} intake. Regarding energy intake, the findings are in agreement with the present study, with daily mean caloric intake ranging between 1,300 and 1,700 kcal in older adults with similar BMIs ($24\text{-}27 \text{ kg m}^{-2}$). However, a sub-group analysis of the energy intakes and body composition of those who consumed $< 0.8 \text{ g protein kg bw}^{-1}$ intake, would have provided a better insight and a direct comparison with the current study.

The only study with relatively comparable data to the current one is that of Muscariello et al. (2016). In a total of 130 obese Italian women (> 65 years old; $\text{BMI} \geq 30 \text{ kg m}^{-2}$), 104 of which had low muscle mass, mean daily energy intake was $\sim 1,800 \text{ kcal}$ with 15%, 55% and 30% contribution from protein (68 g), fat (248 g) and carbohydrates (60 g), respectively (Muscariello et al. 2016). Similar relative intakes were reported in the present study, especially with respect to protein (section 6.2). Total daily energy intake was higher compared with the present study, but this may

be explained by the smaller body size of the current participants (with a BMI of approximately 27 kg m⁻²). Muscariello et al. (2016) commented that the protein content corresponded to 0.7±0.2 g protein per kg of desired bodyweight per day, however, it was not fully explained how such ‘desired’ body weight was calculated. Given that desired bodyweight must be lower than their actual weight (since BMI >30 kg m⁻²), then the actual relative protein intakes must have been lower than 0.7±0.2 g kg bw⁻¹. Therefore, there is relative agreement between studies highlighting that relative protein intakes may be low even when there is a surplus of energy in sarcopenic obese older cohorts.

Although there are some preliminary findings for low protein intakes proportionally to energy intake in sarcopenic obesity, it is suggested that direct comparisons should be approached with caution, since there are considerable variations in protein intakes across study cohorts. Therefore, direct causation cannot be established.

8.3 Blood markers

This section discusses changes in the following blood markers 25(OH)D, IGF-1, ALP and hsCRP. Although the sample size was small in the current study, some numerical changes were noticed, which may be of clinical importance. Creatinine and TSH concentrations were both within the normal range both at baseline and at post-intervention for both groups, with no large fluctuations noted. Urea increased slightly above the reference range in one participant from the diet and exercise group, however, this small change was anticipated especially in the diet group who received supplementary protein (Frank et al. 2009).

In the current study, 25 µg vitamin D3 was administered to both groups EOD (~ 10 µg day⁻¹) to ensure adequate vitamin D intakes and to avoid potential confounders associated with low serum 25 (OH)D, such as poor physical performance in older adults (Wicherts et al. 2007; Kim et al. 2011; Verlaan et al. 2017). There is a strong and inverse relationship between sarcopenia and serum 25(OH)D in older adults, with the association remaining significant even after adjusting for factors such as BMI, age, sex, smoking and physical activity (Kim et al. 2011), however, it should be highlighted that association does not imply causality. In the current study the change in both groups was similar after four months of supplementation. In EX it increased by 15 (-1, 31) nmol L⁻¹ and in EXD by 19 (9, 27) nmol L⁻¹ (*section 6.9*). All participants were supplemented, with the exception of one individual, who had to discontinue with vitamin D supplementation, and eventually experienced a noticeable drop in serum concentrations. Another participant experienced a decline in 25(OH)D, however they reported to have consumed vitamin D as per instructions. Although, the decline could be accounted for by seasonal variations (baseline measurement was taken in October and the final measurement in January) this was not observed in any other participants of the same group. Therefore, it could be due an individual response to vitamin D or more likely due to poor adherence to the protocol.

In a 12-month RCT, Grimnes et al. (2017) administered to 275 postmenopausal women with osteopenia/ osteoporosis doses of Vitamin D of ~ 20 µg day⁻¹ vs 163 µg day⁻¹ for one year. Serum 25(OH)D in the high dose group increased by 99.4±31.9 nmol L⁻¹ (from 64.7± 21.4 nmol L⁻¹ at baseline). The increase in the normal-dose group was 17.7± 16.9 nmol L⁻¹ (from 64.1± 20.0 nmol L⁻¹ at baseline) and was numerically comparable to the increase observed in the present study, despite a lower dose supplemented in the current protocol. Perhaps baseline concentrations play a role in the responsiveness to Vitamin D supplementation, since 20 µg Vitamin D3 day⁻¹ for three and six months was recently reported to increase serum 25(OH)D by approximately 32 – 36 nmol

L⁻¹, in pre-frail and frail participants > 65 years with baseline concentrations of ~ 36 nmol L⁻¹ (Vaes et al. 2018). Based on the current findings and others (Grimnes et al. 2017; Vaes et al. 2018), it can be suggested that daily supplementation with 10-20 µg (or 25 µg EOD) Vitamin D3 is adequate to increase serum concentrations by ~ 15-30 nmol L⁻¹, depending on baseline levels.

More importantly, findings by Grimnes et al. (2017) highlight the lack of significant changes in handgrip and knee extension strength, balance and quality of life between or within the two groups over time. This is in agreement with Vaes et al. (2018) who also reported no significant improvements in knee extension/hand grip strength, TUG test, SPPB scores, gait speed, and five repeated chair stands in the absence of exercise training. However, these findings do not parallel those from a meta-analysis by Muir and Montero-Ontasso et al. (2011), who concluded that daily doses of 20-25 µg can produce favourable changes in strength and balance in older adults, even in the absence of exercise. A recent meta-analysis has shown that daily administration of vitamin D2 or D3 in doses 10-25 µg may not improve strength but may offer small but statistically significant improvements in the TUG test by 0.75 s (Dewansingh et al. 2018). Such discrepancies between studies may be due to genetic polymorphisms that can predispose certain individuals to better or worse outcomes depending on the individual's genotype and vitamin D dosing regimen (Grimnes et al. 2017). In addition, another meta-analysis has suggested that vitamin D may be effective in improving strength and function only in older adults with baseline levels < 30 nmol L⁻¹ (Beaudart et al. 2014). This is consistent with Stockton et al. (2011), who noted that improvements in strength are not expected in those with baseline concentrations > 25 nmol L⁻¹, however significant improvements may be seen in those with < 25 nmol L⁻¹. This could provide a plausible explanation for the lack of benefits following vitamin D supplementation in the studies by Grimnes et al. (2017) and Vaes et al. (2018), and suggest that the changes noted in the current study were due to the exercise protocol and not the vitamin D supplementation, since all baseline serum

concentrations were $> 30 \text{ nmol L}^{-1}$. Even those participants who experienced a decrease in serum 25(OH)D, noted numerical improvements in physical function at the end of the study.

Apart from changes in strength and functional performance, vitamin D has been implicated in health conditions commonly seen in older adults. In a recent study examining the relationship between vitamin D status and heart disease, it was found that a low serum 25 (OH)D concentration was associated with a 12-fold increase in risk of heart failure (odds ratio [95%CI]: 12.19 (4.23–35.16) (Porto et al. 2017). What is also noteworthy from this study, which was conducted in adults ≥ 60 years, is the fact that the threshold for low serum Vitamin D was set at 75 nmol L^{-1} and not 50 nmol L^{-1} which is the current threshold for adequate blood 25(OH)D concentration in the UK. If the threshold was to increase to 75 nmol L^{-1} , only two participants in the current study would have met that target at baseline. Accordingly, after the supplementation period four participants did not attain a concentration of 75 nmol L^{-1} .

Another important biomarker is IGF-1, a mediator of growth hormones that is associated with physical and cognitive function in older adults (Doi et al. 2016). In the present study a median percent change of approximately 10 % was noted in EXD, whereas the EX group (control) experienced negligible changes. Overall variations in serum IGF-1 were detected at baseline with values ranging between 54 ng mL^{-1} and 101 ng mL^{-1} , which perhaps may be accounted for to a certain degree by baseline differences in body composition, dietary factors and physical activity levels between participants (Heaney et al. 1999; Arnarson et al. 2015; Bjersing et al. 2017). Although no participants had serum IGF-1 values outside the normal range at baseline, five participants exhibited concentrations $< 82 \text{ ng mL}^{-1}$, which may reflect an increased risk for disability as suggested by Doi et al. (2016). In the study with older healthy adults IGF-1 was found

to be an independent predictor of physical and mental impairment, even after adjusting for factors such as physical activity and cognitive status. Doi and colleagues also noted that those in the lowest quartiles for IGF-1 (Q1: $\leq 82 \text{ ng mL}^{-1}$ and Q2: $83\text{-}100 \text{ ng mL}^{-1}$) had a significantly higher risk for disability compared to the highest quartile (Q4: $\geq 120 \text{ ng mL}^{-1}$) after approximately 2.5 years of follow up.

Supplementation with 15 g of EAAs alone can significantly increase IGF-1 in healthy older women (Dillon et al. 2009). Considering that the content of intact protein is $\sim 40\text{-}45\%$ EAA, 15 g EAA would correspond to $\sim 35 \text{ g}$ protein (Ferrando et al. 2010). In the current study a bolus dose of 50 g milk protein was administered. Increased consumption of dairy products, particularly milk, has been shown to produce similar results in circulating IGF-1 concentrations in older adults (Heaney et al. 1999). Increased milk consumption ($\sim 16 \text{ g}$ of additional dairy protein $\cdot \text{day}^{-1}$) can significantly raise serum IGF-1 by 10 % (Heaney et al. 1999). Similar increases have also been noted after the introduction of 45 g whey protein to habitual diets of older Caucasian adults (overall protein intake increased by 17 g day^{-1}), which resulted in significantly higher serum IGF-1 (from $10.74 \pm 0.41 \text{ nM}$ to $11.37 \pm 0.53 \text{ nM}$) (Kerstetter et al. 2015).

Although increases in IGF-1 concentrations were expected due to increased dairy protein intake, it has also been shown that a hypocaloric diet can negatively affect IGF-1 concentrations in both the short and long-term (Musey et al. 1993; Fontana et al. 2008). However, according to Musey et al. (1993), a high protein diet can in fact increase IGF-1 during two weeks of severe caloric restriction in obese adults (68% contribution of protein to total energy intake with a $\sim 75\%$ energy reduction), whilst also maintaining nitrogen balance. This effect was observed in the high-protein diet but not in the high-fat or high-carbohydrate diet, both of which led to decreased IGF-1 concentrations and negative nitrogen balance. The authors proposed that serum IGF-1 is closely

related to protein intake, nitrogen balance and muscle mass. It has been shown that even after chronic energy deficits (1-6 years), a diet providing a small caloric restriction of $\sim 300 \text{ kcal day}^{-1}$ does not negatively impact serum IGF-1 as long as protein intake is adequate ($\sim 17\% - 24\%$ of TEI) (Fontana et al. 2008). To examine the relationship between protein intakes relative to body weight and IGF-1, Fontana and colleagues measured changes in serum IGF-1 between adults consuming $\sim 0.8 \text{ g kg bw}^{-1} \text{ day}^{-1}$ (10% of TEI) vs $\sim 1.7 \text{ g kg bw}^{-1} \text{ day}^{-1}$ (24% TEI). Although energy was restricted by $\sim 200 \text{ kcal}$ more in the high-protein compared to the moderate-protein group, serum IGF-1 was significantly higher in the high-protein group after six years, suggesting that protein intake may be a more important predictor of changes in IGF-1 than ER. Although the aforementioned studies were conducted in young and middle-aged participants, it is plausible to hypothesise that despite the energy deficit in the current study, the increased protein intake in EXD accounted for the more noticeable change in IGF-1. Nevertheless, energy and dietary protein intake aside, exercise training is another variable that could have potentially affected circulating IGF-1.

A study has suggested that IGF-1 concentrations may in fact decrease in overweight and obese older adults undergoing an exercise routine, despite improvements in lean mass and physical function (Arnarson et al. 2015). After a 12-week resistance exercise trial with older adults, Arnarson and colleagues reported that IGF-1 decreased significantly by $\sim 6 \text{ ng mL}^{-1}$ (from 112.1 ± 35.6 to $106.1 \pm 35.2 \text{ ng mL}^{-1}$). In addition, although at baseline the amount of lean mass was positively associated with serum IGF-1, this changed to an inverse association at the end of the study, with those experiencing the biggest increase in IGF-1 not gaining as much lean mass as those who actually experienced a decrease in serum IGF-1. However, this paradoxical finding should be interpreted with caution, since there were large inter-participant variations. Namely, in 59% of the participants serum IGF-1 decreased, whereas in 39% of them IGF-1 increased, with an

overall net decrease of ~5%. Some of this variation may be explained by the adiposity of participants, since the leaner participants tend to experience a decrease in IGF-1, whereas those with higher fat mass, do not experience significant changes after 15-weeks of resistance training (Bjersing et al. 2017). The reduction in IGF-1 with exercise training has also been reported elsewhere in the literature (Schmitz et al. 2002; Nindl et al. 2004). The authors of these studies have speculated that it may occur at the initial stages of active muscle tissue synthesis, whereas it may plateau around week 15, or even increase in the long-term (>15 weeks) (Schmitz et al. 2002). Nindl et al. (2004) hypothesised that although total IGF-1 may decline after 12 weeks of resistance exercise, free IGF-1 concentrations may remain stable.

To the researcher's knowledge, Chen et al. (2017) is the only study to include IGF-1 data in sarcopenic obese older adults. The study showed that the type of exercise training can have a significant effect on IGF-1 concentrations, with both resistance exercise and mixed resistance-aerobic training resulting in significantly higher concentrations than the control group (no exercise). Moreover, the mixed-exercise group experienced significantly greater serum IGF-1 compared to the aerobic-only and control group, whereas the resistance-only group experienced a significantly higher IGF-1 compared to control only. However, in the current study the exercise protocol was similar in both groups, therefore it is not likely to have confounded the results. Moreover, the absolute concentrations reported in the study by Chen et al. (2017), with values ranging from ~ 3-5 ng mL⁻¹, are substantially lower than what the current study and other studies have reported (Schmitz et al. 2002; Nindl et al. 2004; Fontana et al. 2008; Dillon et al. 2009; Arnarson et al. 2015). Therefore, the findings of that study need to be interpreted with caution.

In the absence of large changes in IGF-1 in the control group (EX) in the present study, it can be hypothesised that the increase in IGF-1 in EXD is likely to be accounted for by increased protein

intakes, as suggested by Dillon et al. (2009) and Fontana et al (2008) who supported that protein intake is a key factor in IGF-1 modulation. This finding is also in accordance with Kerstetter et al. (2015) who noted that daily incorporation of 45 g whey protein in the diet for 18 months can increase IGF-1 significantly more than an isocaloric carbohydrate-rich supplement. Even smaller manipulations in dairy protein intake (e.g. additional 16-20 g dairy protein daily) can significantly increase IGF-1 concentrations (Heaney et al. 1999). The lack of numerical changes in the control group in the current study may be accounted for by reasons discussed earlier (Schmitz et al. 2002), or more likely by the lack of high intensities employed in the current programme. This notion has also been corroborated by Izquierdo et al. (2006), who suggested that exercise intensities of 60 to 70% 1RM may not have the potential to induce significant changes in serum IGF-1 unless all sets are performed to volitional failure, or alternatively, if the exercise volume is very high (Izquierdo et al. 2006).

To better understand the relationship between circulating IGF-1 and changes in body composition, it would have been interesting to have performed a third test mid-point between baseline and follow-up. Moreover, although total serum IGF-1 concentrations can provide meaningful explanations, it has also been suggested that measuring free IGF-1, and specific IGF complexes (e.g. IGF binding proteins such as IGFBP-3 and IGFBP-5) can perhaps offer more insightful information in terms of musculoskeletal growth and metabolic/physiological adaptations (Izquierdo et al. 2006; Yakar et al. 2009). Moreover, assessment of GH responses could potentially provide a better interpretation, especially considering that changes in body composition and body fat, can affect serum IGF-1 concentrations by modulating the secretion of GH (Savastano et al. 2014).

Due to the small sample size, statistically significant changes could not be established for serum ALP within the current study, albeit small numerical alterations were noted in both groups. Alkaline phosphatase is routinely used in clinical tests as an indicator of hepatic function and bone metabolism as well as intestinal and pancreatic function. Although, total ALP contains a mixture of the isoenzymes from all these organs, the serum total ALP concentration is primarily a marker of bone health and secondly a marker of liver health, since these are the tissues from which most of the isoforms originate (Mukaiyama et al. 2015). A high serum ALP is associated with an increased risk of low bone density (Hwang et al. 2017). Adults aged ≥ 80 years exhibit higher serum ALP compared to adults ≤ 60 years, with increases in ALP indicating increased bone turnover and osteopenia (Mukaiyama et al. 2015). In the current study, the small within-group alterations in ALP may indicate that bone metabolism was probably not affected by the dietary regimen. However, as mentioned, the sample size was too small to draw clear conclusions.

Heaney et al. (1999) assessed the effect of protein supplementation on ALP in older adults. The authors reported that the addition of three servings of milk to habitual diet (accounting for a change in protein intake by approximately +15-20 g daily) decreased ALP concentrations by 9%, which was a significant change over time. However, unequivocal conclusions cannot be reached since ALP concentrations declined similarly in the control group, with no significant differences between groups, indicating that protein intake was not solely responsible for the decrease in ALP.

As Filipowicz et al. (2013) have stated, total serum ALP is directly associated with C-reactive protein, inflammation and higher mortality risk. It was also suggested that in the absence of bone or liver disease, the relationship between total ALP with CRP-related inflammation is mediated by fractions of isoenzymes other than bone or hepatic. Although the sample size of the current cohort was too small for conclusions to be drawn, a small numerical decline in both ALP and

hsCRP was seen in the exercise and diet group (EXD), whereas the respective markers in the control group either remained unchanged or increased marginally.

High-sensitivity CRP is a blood protein that increases with inflammation and is linked to higher risks of sarcopenia, arteriosclerosis and CVD development (Hida et al. 2017), with a strong association with CRP (Helal et al. 2012). Moreover, hsCRP is associated with obesity (defined as high %BF) and sarcopenic obesity (defined as high %BF and low SMI) (Yang et al. 2015). Despite the small sample size, this is the first study to examine the effect of a lifestyle intervention on hsCRP in Scottish older sarcopenic-obese community dwellers. The changes in hsCRP in EX were negligible, whereas EXD experienced a median (% median) change of -0.8 mg L^{-1} (-30%) (Chapter 6, *section 6.9*). Although it has been shown that there is an inverse relationship between grip strength, physical function and hsCRP (Granic et al. 2017; Hida et al. 2017), associations do not always indicate causality. For example, a change in strength over time does not necessarily imply changes in hsCRP (Granic et al. 2017). The findings of the current study suggest that the driving factor for changes in hsCRP was fat/weight loss and not changes in physical function.

In a trial with adults ≥ 50 years, Nicklas et al. (2015) reported significant changes in bodyweight (-6.5 kg) and similar median (% median) declines to the current study in hsCRP [-0.4 mg L^{-1} (-28%), $p < 0.05$], after a weight-loss regimen. On the other hand, in another study with sarcopenic obese adults, it was noted that exercise alone did not significantly reduce CRP even in the presence of significant improvements in physical function (Huang et al. 2017), which is in agreement with the current findings and those of Kim et al. (2016a). Kim and colleagues reported improvements in physical function of sarcopenic obese older adults following exercise training, but in the absence of significant body fat losses there was no statistical change in hsCRP.

Another parameter that should be taken into account is abdominal obesity. Van de Bool et al. (2015) have shown higher hs-CRP concentrations in sarcopenic adults with abdominal obesity compared to sarcopenic counterparts with no abdominal obesity. Although it has not been statistically confirmed in the present study, the diet and exercise group experienced a greater reduction in sagittal abdominal depth, which could perhaps explain to some extent the decline in hsCRP. Thus, reductions in anthropometric markers of central obesity may have a favourable effect on inflammation. This hypothesis would be in agreement with the findings of van de Bool et al (2015) and Schrager et al. (2006), who proposed that obesity (particularly central obesity) can directly mediate an inflammatory response.

Therefore, it can be proposed that a multi-angled approach for the management of sarcopenic obesity is necessary; that is, attenuating inflammation through decreases in body fat, as well as improving physical function through exercise training. A decrease in hsCRP in the current cohort would theoretically indicate a lower risk for CVD, this however, should be confirmed in large cohorts following standardised operational protocols once definitions of sarcopenia and sarcopenic obesity have been established (Wang et al. 2017).

8.4 Health-risks associated with higher protein intakes and energy deficit

In the current study, no evidence of impaired kidney function was observed. Serum creatinine concentrations were within normal levels at baseline and after 16 weeks of a high protein diet providing ~ 1.4 g protein kg bw⁻¹ day⁻¹. This is in agreement with Mikusova et al. (2016), who reported no significant changes in renal function in older sarcopenic adults after six months of protein intakes of ~ 1.5 g kg bw⁻¹ day⁻¹.

In terms of bone health, no substantial changes were noted in ALP, which combined with the increased IGF-1 concentrations in EXD suggests that the current protocol is not likely to have negatively affected bone health. Kerstetter et al. (2015) assessed the effect of daily administration of 45 g whey protein on both bone health and kidney function in older Caucasian adults. After a period of 18 months, there was no difference in bone density between the group receiving protein vs their counterparts receiving an isocaloric carbohydrate-rich supplement, despite a significant change in absolute protein intake by $\sim +17$ g and in relative protein intake from ~ 1.1 g kg bw^{-1} to 1.3 g kg bw^{-1} . Bone mineral density at the sites of interest (e.g. lumbar spine, femoral neck and total hip density) did not change either between or within groups. Moreover, the high protein group exhibited a significant increase in lean mass and serum IGF-1 at the end of the 18 months. As expected, a significantly higher concentration of urinary urea was noted in the protein group, however, renal function was normal and not different from baseline. These findings are in agreement with systematic reviews and meta-analyses reporting no detrimental effects in response to protein intakes higher than 0.8 g kg bw^{-1} (Darling et al. 2009; Shams-White et al. 2017; Wallace and Frankenfeld 2017). In fact, protein intake over the current recommendations of 0.8 g kg bw^{-1} may offer small but significant benefits by increasing bone mass density, and therefore, potentially reduce the risk of bone fractures (Darling et al. 2009; Wallace and Frankenfeld 2017). However, these were not measured in the current study.

Regarding weight loss-induced impact on bone mass, a recent meta-analysis showed that bone health is inversely associated with relative fat mass (Dolan et al. 2017). Moreover, muscle mass and muscle density are positively associated with bone health and balance in obese older adults (Scott et al. 2018). Since muscle mass was maintained and fat mass losses were noted it could be speculated that the current protocol did not have a detrimental effect on bone health, however DXA assessments would need to confirm that. As Heaney et al. (1999) have noted even a $\sim 1 - 2\%$

decrease in ALP over 12 weeks can indicate a significant improvement in bone metabolism. Although a numerical decrease of a similar range was noted in the EXD group, this hypothesis cannot be corroborated in a small sample size. For a more valid quantification of bone turnover the bone specific ALP (BSAP) isoenzyme should be tested, as BSAP is not affected by the diet or circadian variations (Seamans et al. 2011; Roudsari et al. 2012). However, a drawback of BSAP is that it is quite expensive to quantify and is therefore, not used frequently as a diagnostic marker (Mukaiyama et al. 2015).

Chapter 1 has presented the acute effect of whey protein ingestion on impaired glucose uptake and insulin resistance as reported by Smith et al. (2015). Recently, Smith et al. (2016) conducted a long term study which found that a high protein diet during a period of energy deficit may lead to insulin resistance by impairing the ability of muscle to utilise glucose, and therefore, may cancel out the weight loss-induced metabolic benefits. However, there were some conflicting findings that need to be corroborated in future studies. For example, there were no differences between the low- and high-protein groups in fasted glucose, insulin levels, intrahepatic triglyceride content, intra-abdominal adipose mass or free fatty acid concentrations (Smith et al. 2016). Such differences would indicate metabolic impairments and insulin resistance (Alipour et al. 2007). In fact, the high-protein group experienced 45% lower losses of lean mass, which was a positive effect of the high protein regimen (Smith et al 2016). Although the present study used milk protein and not whey, a test to assess the effects of exercise and high protein intake on glucose metabolism could have been performed e.g. a glucose tolerance test. However, assessment of glycaemic control would require participants to present to study sessions in a fasted state, and would therefore, confound strength and functional tests, not to mention be an extra burden for participants. To the best of the researcher's knowledge, no findings have been disseminated to imply a negative metabolic response to milk protein. Even in type II middle-aged and older

diabetic patients, the acute protein-induced insulinemia can favourably modulate post-prandial glycemia (Manders et al. 2014), and improve fasting and post-prandial glycemia, glycated haemoglobin and waist circumference in the long-term (Jakubowicz et al. 2017).

8.5 Strengths, limitations and challenges of the intervention study

The small sample size was the most profound limitation of the intervention trial. Although some changes (e.g. fat mass) were numerically noticeable (as well as clinically relevant), it is possible that they would reveal significant differences between/within groups had the sample size been large enough. Therefore, robust conclusions could not be drawn. Thus, the interpretation as to whether it was the dietary or the exercise regimen that accounted for changes reported was not based on the presence of statistical significances, but based on comparisons with other studies using similar methodologies and assessing similar outcomes in older and/or sarcopenic obese participants.

Although the costs associated with the study were low, the budget and resources that the researcher had at his disposal was minimal for a clinical trial of this magnitude. The protein supplements were the main asset of this study and had to be purchased from a supplement company. As a result, the available budget was spent in its entirety for the protein supplements alone. The available budget would allow for a maximum of ~10 participants to complete a full 20-week protocol or ~13 participants for a 16-week protocol. Equally important was the fact that the final prevalence of sarcopenic obesity in this cohort (12%) meant that in order to recruit > 50 participants (as per initial target), a minimum of 416 older adults were required to be screened, which turned out to be an unrealistic goal given the lack of available participant database.

The lack of an established pool of potential participants for studies was therefore a limitation, which impacted heavily on time and resources used at the beginning and throughout the course of the study. This issue became even more challenging considering that within QMU research usually involves young healthy cohorts. In light of this, the researcher established a small volunteer database, thus creating better prospects for future recruitment purposes. However, apart from recruitment, the main researcher of the study had to execute all practical applications of this study, including screening, dietary assessments, diet plans, data collection throughout the study (including the blood tests), and delivery of the exercise classes. On top of that, the researcher liaised with the supplement company, purchased the supplements and arranged for their delivery and distribution to participants.

Habitual physical activity data could have been collected throughout the current study to assess potential changes in habitual physical activity levels, including sedentary time. Moreover, heart rate monitors or accelerometers could have been worn during exercise classes to estimate the energy expenditure during exercise, which would allow for a better understanding of how the exercise classes contributed to daily energy expenditure. Furthermore, there was a lack of specific data regarding regional body composition changes due to limitations of the BIA device, which did not allow for better quantification and interpretation of body composition changes, in particular visceral fat mass and appendicular lean mass. Moreover, regional analysis of muscle mass, would have allowed for a more dimensional assessment of muscle quality, e.g. hand grip strength per unit of arm lean mass (Liao et al. 2017b).

Studies with older adults involving dietary and/or exercise interventions are likely to report drop-out rates > 20%, as observed in a systematic review by Shams-White et al. (2017). In fact in studies with sarcopenic or sarcopenic obese older adults following an exercise or nutritional intervention,

drop-out rates of >30% have been documented (Wouters- Wesseling et al. 2003; Chen et al. 2017), which are in line with the drop-out rates reported in the current study. With regard to compliance with dietary protocols, Shams-White et al. (2017) have demonstrated that in most studies involving protein supplementation compliance is <80%. Therefore, the compliance rate of 80% for the overall diet and 92% for the protein drink in the current study was overall very good. This underlines the practical benefit and sustainability of providing a flavoured ready-to-drink protein supplement.

Although the study was delivered in its entirety by one person (the primary researcher) this ensured consistency in day-to-day tasks, adherence to protocols, direct communication with the participants and the ability to resolve issues swiftly. Moreover, the relatively small number of participants per exercise class ensured that participants received individual feedback and were paid close attention to, which may not be feasible in large multi-centred studies where many trainers/researchers are involved and may thus, lack consistency. This also applies to the techniques used for anthropometric measurements, functional tests as well as the design of nutritional plans and implementation strategies.

In the current study there was no conflict of interest as supplements were purchased without sponsorship from a company. The exercise classes were performed in classrooms resembling those in community centres, without the provision of any specialised exercise equipment. The only items available were chairs and elastic bands. The latter can be purchased at a low cost, and do not require any storage space or physical exertion to be moved from location to location. In addition, the supplements used are widely available to the general public, at a reasonable cost. Thus, the whole protocol can be easily adopted at a low cost, which is vital for the sustainability and

practicality of community-based interventions. Moreover, this study provides data which can inform cost-analysis components of larger trials.

Although the importance of a healthy lifestyle has been recognized globally, it has been documented that approximately half of older adults are not likely to meet the targets for physical activity (PA) in developed countries (Hallal et al. 2012), including Scotland as discussed in Chapter 1. The reasons for this behavior may lie in personal beliefs and environmental factors, such as peer interaction and encouragement from others (Franco et al. 2017). For example, during the recruitment phase of the intervention trial, when the primary researcher was attending events for older adults, a common response from older adults who had an apparent physical impairment (e.g. slow gait speed, use of walking aids, muscle weakness) was that *'I am doing a lot better than people of my age who use wheelchairs/ electric scooters, or are bed bound, therefore, I am doing well'*. It has been documented that older adults often believe that the consequences of ageing are inevitable, and just by living outside of institutionalisation should be considered as something positive for an older person (Bardach et al. 2016). In fact, older adults who accept age-related loss of muscle, function and strength that may be accompanied by conditions such as obesity, dyslipidemia and hypertension, tend to normalize their condition and therefore accept it, without feeling the need for improvement (Bardach et al. 2016).

In general, people would often make enquiries to this research project after their GP had indicated that certain parameters should be improved (e.g. their lipid profile, or blood glucose concentration), thus they had specific reasons for participating. Furthermore, people who visited QMU labs for the screening tests, and were provided with specific body composition values (e.g. %BF or SMM) felt motivated to start exercising, because they felt they could quantify their

problem and had a reference point which would help them monitor their progress. As Bardach et al. (2016) has suggested, although the training of health professionals can be improved by putting emphasis on healthy ageing (than merely treating the age-related conditions with medication), their interaction with older adults can offer more than the obvious treatment. That is, by conducting health assessments (e.g. weight, waist circumference, blood tests) they can provide the older adults with a specific plan of what should be addressed in order to reduce health risks.

Some potential participants in the current study were worried about exercise intensities before commencing the programme. For the same reason, at the end of the study some individuals were timid about attending the exercise classes that were set up at QMU sports centre for those who wanted to keep exercising. That is, although they had a positive experience from the research programme they were concerned whether they would be able to keep up with the ‘new pace’. One participant, who dropped out of the study, mentioned that she was not encouraged by her family members to continue with the trial, after taking ill by a seasonal flu. Her family advised her that an exercise/nutritional programme was not suitable for an older person, and would hinder recovery. Another participant who dropped-out of the study, reported at QMU facilities after a holiday break with a sore neck, and was hesitant to continue in fear of aggravating her trapped-nerve. The inability to keep up with training paces can lead to a sense of incompetence and low self-esteem and is one of the key barriers to exercise, not only due to the inability of some to keep up with the higher physical demands, but also due to perceived pain and distress, fear of falling and joint damage (Simmonds et al. 2015). Further, advice often received by peers/family/clinicians to avoid physical activities and ‘*take things easy*’ has been documented in the literature as the main barriers to exercise in older cohorts (Franco et al. 2017).

Further, encouraging older adults to follow a weight-loss diet and to consume a high-protein food can also be challenging, as previously documented by Appleton et al. (2016) and Bardach et al. (2016). Apart from reductions in chemosensory abilities (i.e. changes in palatability and taste with age), main barriers include practical issues. For example, the effort required to prepare food, convenience of consumption and affordability, as well as reduced spoilage and food wasting. Although older adults tend to initially reject the idea of fortified foods, they will regularly consume foods they have tasted and found acceptable, or have been commercialised for use only by older adults due to proposed health benefits that are related to older age (van der Zanden 2015). Similarly, older adults appear to be negatively affected by previous unsuccessful experiences (Bardach et al. 2016). For instance, after failed attempts to lose weight (which may have occurred more than once), individuals may subsequently feel that losing weight via dietary means is not something achievable and should not be pursued further. Moreover, mixed messages regarding diet can lead to confusion in older adults surrounding food choices, as well as decrease interest in healthy eating (Best and Appleton 2013).

Finally, the location of the exercise classes was also a barrier to adherence to the trial, since the classes were not based at close proximity to Edinburgh's city centre. Although the location could serve well the local communities, it was perhaps not ideal for those living in Edinburgh. This further limited the potential participant pool to only those who could walk to the premises, or use public transport/ private means. One of the individuals who decided to participate, despite residing at the opposite side of Edinburgh, recorded low attendance rates. As reported, the individual was keen to participate although she had difficulties reaching QMU premises. Commuting time was approximately two hours and required the use of more than one means of public transport. Moreover, the same participant was also caring for her spouse. Indeed, competing priorities (e.g. caring for a family member, spending time with family, and social commitment), long distances

and multiple means of transport have also been documented by Franco et al. (2017) as key barriers for older adults to participate in physical activities.

8.6 Recommendations for future research

Regarding nutrition interventions, apart from single ingredients/foods, recent research paradigms are rightfully shifting towards more multi-angled approaches, embracing the properties of various foods and/or supplements in order to help older adults augment their body composition and functional capacity. A recent study by Bell et al. (2017), has highlighted the importance of combining different nutritional supplements that can work in synergy to favour muscle growth and physical function in older adults even in the absence of exercise. Namely, whey protein (30 g), creatine (2.5 g), vitamin D (500IU or 12.5 µg), calcium (400 mg), and poly-unsaturated n-3 fatty acids (1.5 g) were consumed in a dietary supplement twice a day for six weeks by healthy adults aged over 60 years and with a mean BMI and % body fat of 28 kg m⁻² and 33%, respectively. As creatine can enhance muscle strength and function in older adults (Devries and Phillips 2014) it is a supplement that could potentially complement a high-protein regimen in studies with sarcopenic obese individuals. Despite the positive initial results (increased lean mass by ~ 0.7 kg mass) (Bell et al. 2017), the practicality, sustainability and adherence to multi-supplement protocols should be evaluated in the long term.

In another multi-component study, daily consumption of 10 g whey protein with 10 µg vitamin D3 and at least 2.0 g DHA + EPA resulted in significantly higher lean mass (~1.9 kg), improved lipid profiles and lowered fatigue in 45 adults with COPD (mean age ~69 years) over a period of 12 weeks (Calder et al. 2017). Fish oils and n-3 polyunsaturated fatty acids (PUFAs) are regarded as potentially useful ingredients for the sensitisation of ageing muscle to anabolic stimuli such as protein feeding. For example, the ingestion of fish oils for eight weeks has revealed significant augmentation of anabolic responses to hyperaminoacidaemia and hyperinsulinaemia after acute protein feeding, in both young/middle aged (Smith et al. 2011a) and older adults (Smith et al.

2011b). The daily dose used in these studies was 4 g (~1.9 g DHA and 1.5 g EPA), which resulted in significant increases in mTOR and p70S6 kinase phosphorylation levels, as well as higher acute muscle synthetic responses after eight weeks of supplementation.

Although these findings are promising, the main limitation is that most studies have been conducted in the short-term, with only a few protocols longer than 12 months in duration (Byrne et al. 2016; Kim et al. 2016b). In addition, as shown in the current study, it is not realistic to expect perfect attendance rates to exercise classes mainly due to illness, or other commitments. Considering also that significant muscle losses are likely even during very short periods of inactivity/immobilisation, examining the effects of lifestyle changes for a few weeks or even months under ‘ideal’ conditions may not be the most pragmatic paradigm for the assessment of lifestyle programme effectiveness and sustainability. Therefore, long-term studies are required that will utilise protocols under more realistic conditions. A way to potentially overcome the issues associated with short-term inactivity (e.g. muscle atrophy or loss of strength) would be the use of electromyostimulation (EMS) devices. These devices, if used prior to protein feeding, can significantly increase muscle protein synthesis rates in older adults by ~18% (Dirks et al. 2017). In the long-term they can increase muscle mass and strength, while promoting fat loss in sedentary or osteopenic older adults (Kemmler and Stengel 2013; Stengel et al. 2015), and also in sarcopenic obese adults who cannot participate in exercise training [SMI/BMI: +0.02 (95%CI: 0.01, 0.03); %BF -2% (-1.40, -2.68); grip strength: +1.9 (1.0, 2.8kg)] (Kemmler et al. 2017b; Kemmler et al. 2017c). Therefore, it should be elucidated whether a combination of resistance exercise with the use of EMS on ‘rest days’ or days of low activity/inability to exercise can enhance the effect of protein feeding, which may result in more pronounced effects than resistance exercise and diet alone.

In relation to above, in a hypothetical 12-month programme the initial month(s) could be used to familiarise participants with exercise protocol and employ a more conservative approach in terms of dietary changes. The period would focus mainly on exercise technique, balance, proprioception and flexibility. The second phase would focus more on strength, endurance and aerobic exercises, introducing a slight caloric deficit (~200-300 kcal) ensuring an adequate carbohydrate intake. The third phase would introduce a moderate caloric deficit (~500 kcal) alongside a high protein intake (~1.5 g kg bw⁻¹) and hypertrophy training with increased exercise volume, and time-under-tension. The next phase would focus on power and agility, maintaining high protein intakes. The final stage would involve exercising at higher training intensities, while the caloric intake would increase to meet the higher energy demand. Vitamin D3 could be supplemented throughout the year at low daily doses (10 µg daily or 25 µg EOD), in addition to omega-3 fatty acids, which could be introduced during the periods of more pronounced energy deficits. Emphasis should also be placed on adequate consumption of fruit, vegetables and whole-grain products in order to improve fibre intake to meet daily fibre recommendations of 30 g day⁻¹ (SACN 2015). Increasing fibre intake may promote diversity in the microbiome and reduce inflammation (Kumar et al. 2016). During periods of inactivity due to illness, hospitalisation or other reasons, an EMS device could be utilised to attenuate muscle atrophy and maintain muscle strength.

Apart from supplementation, it is important to conduct studies that aim to increase protein intakes by using easy to store and prepare high-protein foods. Therefore, foods that are usually preferred by this age group, e.g. high-protein soups as proposed by Donahue et al. (2014), can make the whole process more realistic, palatable and sustainable, with participants more likely to adhere to protocols. For example, egg-based dishes or lean beef could be used more regularly, or in higher quantities, to increase dietary protein (Phillips 2012; van den Heuvel 2017). A portion of 180 g lean beef can provide ~42 g protein which can raise MPS rates significantly higher than a 60 g or

120 g portion (Phillips 2012). However, care should be given to follow dietary guidelines regarding increased consumption of red/ processed meat. Alternatively, smaller portions of chicken or beef with mashed potatoes and vegetables could be enriched with protein by replacing butter with high protein milk (Ziylan 2016). However, such modifications require a certain degree of cooking skills and knowledge of food exchanges (e.g. low protein high energy-density for high-protein low energy-density foods). Such skills and knowledge could be communicated via community-based cooking classes that would place emphasis on healthier lifestyle choices through peer-interactions.

Finally, a better understanding of what the sarcopenic obese adults eat and why they opt for such choices can offer substantial benefits in designing future interventions. Apart from dietary content *per se*, appetite is an important parameter in controlling portion sizes, which can affect energy and macronutrient intake, an area that has been overlooked in sarcopenic obesity. As Hopkins and Blundell (2017) have noted, mechanisms regulating appetite are not yet fully understood even in healthy adults. They suggest that body tissues (especially lean mass) may affect appetite, with fat mass playing a role but to a lesser degree. Therefore, it could be hypothesised that the appetite control mechanisms of sarcopenic obese older adults may be dysregulated in comparison with their eutrophic counterparts, and should be evaluated in future trials. In an attempt to measure satiety ratings in healthy older community-dwellers, Ziylan et al. (2016) found mixed results in response to different portion sizes and protein contents. Based on the theory by Hopkins and Blundell (2017), it could be proposed that body composition may have affected the results. Therefore, it would be worthwhile investigating healthy, sarcopenic, obese, and sarcopenic obese older adults in future to determine whether appetite control mechanisms are dysregulated in sarcopenic obesity. This could inform future nutritional interventions.

Conclusion

In conclusion, the present study is the first study to demonstrate that older Scottish independent-living populations may suffer from increased rates of adiposity and low muscle mass, even with normal BMIs. Body mass index misidentified more than half of the cases of obesity and therefore, the true prevalence of obesity in Scottish older adults may be even higher than what is currently proposed. Classification of obesity based on BMI may also affect the phenotypic characteristics of older groups (e.g. muscle mass and strength) which can limit the pool of participants for sarcopenic obesity studies, and may add ‘noise’ to observational and intervention trials. Central adiposity may affect muscle strength and quality, even for non bodyweight-bearing physical tasks. The rates of sarcopenia may be higher in Scotland compared to England and other European countries, which combined with the increased obesity rates may predispose Scottish older adults to more health limitations. Moreover, if older adults can be sarcopenic and obese (based on low muscle mass/function and high percent body fat), even at normal BMIs, it raises questions regarding the quality of care that they will receive by healthcare professionals.

A simple dietary intervention employing a moderate caloric deficit and increased protein intake via a ready-to-drink protein milk supplement can lead to favourable body composition changes in older adults with low muscle and high adiposity. Protein intakes of $\sim 1.4 \text{ g kg bw}^{-1}$ appeared to be sufficient in attenuating the loss of muscle mass during an energy deficit diet. In addition to increased protein intakes, a mixed exercise programme three days weekly with an emphasis on resistance, aerobic and balance exercises (without the use of sophisticated equipment but only bodyweight exercises and elastic bands) is likely to improve muscle strength and physical function. However, a dietary regimen is necessary to lower fat mass to a degree that is clinically meaningful, which may also attenuate adiposity-related inflammation.

The addition of a milk-based protein supplement does not negatively affect negatively kidney function or bone health, and was well tolerated by an older adult cohort. A low dose vitamin D supplementation protocol in line with the current guidelines can improve serum 25-hydroxyvitamin D in older adults. However, its effectiveness in improving body composition and function in older adults with low muscle and high fat mass is still inconclusive. Despite this, it was shown to help older adults achieve serum concentrations > 50 nM. The combination of these paradigms could be incorporated into longer-duration studies with more participants, and perhaps include more diverse groups e.g. frail, institutionalised or older adults with physical disabilities, who have an unfavourable ratio of fat to muscle mass and poor muscle strength/function.

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Appendix 1 Key summary ACSM recommendations for exercise in older adults (adapted by ACSM 2014).

For Aerobic Exercise:

- Frequency

≥ 3 days / week for vigorous intensity or ≥ 5 days/week for moderate intensity activities.

- Intensity

On a physical exertion scale of 0-10, a score 5-6 would indicate moderate intensity whereas 7-8 vigorous intensity.

- Duration?

Moderate activities should be performed in bouts of at least 10 minutes each for a total of 30-60 minutes a day or 150-300 minutes a week. Vigorous activities can be performed for a total of 20-30 minutes a day for a total of 75-100 minutes a week.

- What types of exercise?

Walking, brisk walking, dancing and jogging. Stationary cycling and aquatic exercise are ideal for those who cannot perform weight-bearing exercises.

Muscle Strengthening/ Endurance Exercise:

- How often?

≥ 2 days / week

- Intensity?

Light intensity for beginners and moderate to vigorous intensity for the more experienced. On a scale 0-10, light intensity is < 5, moderate 5-6 and vigorous 7-8.

- How many?

8-10 different exercises, ≥ 1 set per exercise, 10-15 repetitions for each set.

- Types of Exercise?

Weight-bearing exercises, use of resistance bands, light dumbbells, stair climbing and other exercises engaging the major muscle groups such as legs, back, chest and arms.

Flexibility:

- How often?

≥ 2 days / week

- Intensity?

Stretch until you feel the tightness on the muscle or slight discomfort

- For how long?

Stretch and hold for 30-60 secs

- Type:

Slow movements that either maintain or increase the flexibility of joints for the major muscle groups. Static stretches (i.e. hold and stretch with no rapid movements involved) are preferred.

Appendix 2 Search Strategy

Effectiveness of nutritional and exercise interventions in the management of sarcopenic obesity in older people: a systematic review (SEARCH STRATEGY)

MEDLINE (PubMed)

S1. (MH "Aged") OR aged OR (MH "Adult") OR adult OR (MH "Aging") OR aging OR (MH "Geriatrics") OR geriatric# OR (Over N1 (65 OR 60)) OR old* OR ag#ing OR senior# OR elder*

S2. ((MH "Sarcopenia") OR sarcopeni* OR sarcopenic obesity OR (MH "Muscle Weakness") OR (musc* N2 (weakness OR atroph* OR loss* OR low)) OR (MH "Muscular Atrophy") OR (MH "Frail Elderly") OR (MH "Atrophy") OR frail* OR lean)

S3. (MH "Obesity") OR obes* OR (MH "Overweight") OR overweight OR (MH "Adipose Tissue") OR (MH "Adiposity") OR (high N1 (fat OR adipos* OR BMI OR Body Mass Index))

S4. (MH "Exercise+") OR "exercise*" OR (MH "Exercise Therapy") OR (MH "Resistance Training") OR (MH "Walking") OR (MH "Running") OR ("Physical" N1 ("activit*" OR "training")) OR ("Exercis*" N2 ("endurance" OR "aerobic" OR "resistance" OR "balance" OR "combin*" OR "mixed" OR "multi#modal" OR "eccentric" OR "concentric" OR "isometric" OR "plyometric" OR "program*" OR "regime") OR "protocol") OR (MH "Physical Exertion")

S5. (musc* N2 (mass OR gain OR strength OR size OR cross sectional area OR CSA OR thick* OR power OR growth OR enlarge* OR area OR volume OR hypertrophy OR recovery OR recovery) OR (speed OR gait OR grip OR (MH "Hypertrophy") OR hypertrophy OR (MH "Muscle, Skeletal") OR (MH "Muscle Strength") OR lean mass OR fat free mass OR life N2 quality OR function* OR balance OR flexib* OR dynamic OR fitness OR capacity OR Activities N1 daily living OR ADL#)

S6. (MH "Diet+") OR (MH "Energy Intake") OR (MH "Diet, Protein-Restricted") OR (MH "Diet, Reducing") OR (MH "Diet, Fat-Restricted") OR (MH "Diet, Carbohydrate-Restricted") OR (MH "Diet Therapy") OR (MH "Weight Reduction Programs") OR (MH "Weight Loss") OR (protein* N2 (high OR diet* OR intake OR whey OR milk OR supplement*)) OR (MH "Dietary Supplements") OR (MH "Dietary Proteins") OR supplement* OR Nutrition* OR (MH "Energy Metabolism") OR (Energy N2 (deficit OR reduced OR intake)) OR hypo#caloric OR (MH "Amino Acids") OR (MH "Amino Acids, Branched-Chain") OR (MH "Amino Acids, Peptides, and Proteins") OR (MH "Leucine") OR leucine OR HICA OR Hydroxy?isocaproic acid OR amino acids OR BCAA OR HMB OR methyl N1 butyrate OR creatine

S7. S4 OR S5 OR S6

S8. S1 AND S2 AND S3 AND S7

S9. AB ((MH "Intervention Studies") OR intervention OR Randomi?ed N2 (Control* OR clinical OR crossover OR Trial) OR RCT OR Clinical trial) OR TI ((MH "Intervention Studies") OR intervention OR Randomi?ed N2 (Control* OR clinical OR crossover OR Trial) OR RCT OR Clinical trial)

S10. S8 AND S9 *Limiters - English Language; Human*

Results 600 (22/05/16)

Appendix 3 Overall strengths and rationale of the protocol

Aspect	Strength/ Rationale
Bodyweight exercises initially	<ul style="list-style-type: none"> -Everyone starts at the same baseline -Allows participants with no prior experience to familiarise themselves with the techniques -Minimise the risk of injuries
Mixed Exercise Programme	<ul style="list-style-type: none"> -Allows for improvements in several aspects of fitness that are important in older age e.g. strength, power, flexibility, aerobic capacity, coordination and balance
Use of elastic bands	<ul style="list-style-type: none"> -High Practicality (portable and affordable) -No need for specialized equipment (only an adequately spaced room with chairs) -Can augment muscle mass and strength/function -Safer than free weights -Minimise the 'sticky points' -Can facilitate different intensities and velocities for the concentric and eccentric parts of exercise -Can accommodate the needs for a group of adults with diverse skills and capacity to exercise -Ability to monitor progression
Protein drinks	<ul style="list-style-type: none"> -Help to increase protein intakes even during energy restriction -Protein content similar to what has been found in the literature to stimulate muscle protein synthesis after resistance exercise in older adults -Do not require cooking skills/knowledge -No extra financial burden for the participants -Long shelf life -Commercially available -Practical and convenient -Palatable/ different flavours -May promote satiety, thus better adherence to the energy deficit diet

-Can be used post-workout for rehydration, or in the evening as a pre-bed meal.

Vitamin D supplementation	-Helps minimise confounders related to vitamin D deficiencies -Adheres to UK guidelines.
Overall	-Can be replicated at a community level with minimum resources

Appendix 4.1 Single arm Functional Reach

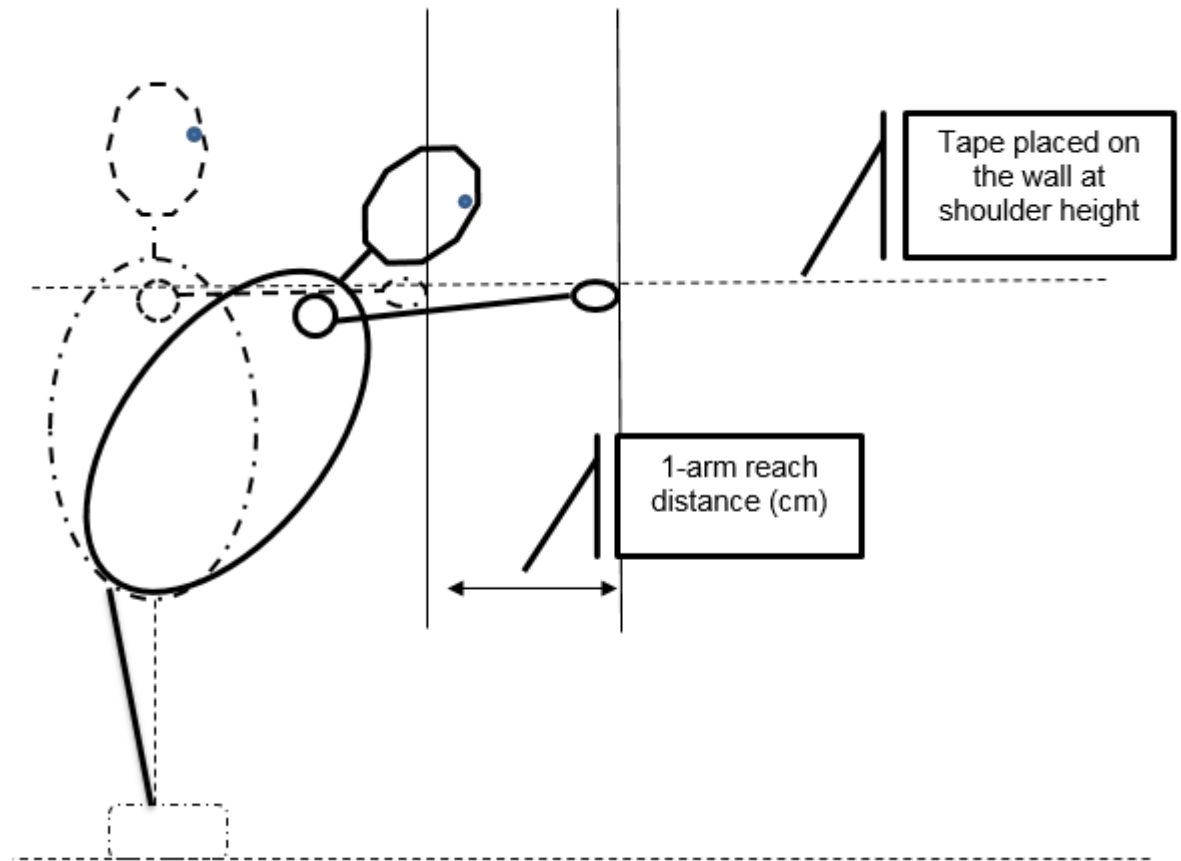


Figure IV-I Body position for the 1-arm functional reach test and measured distance.

Appendix 4.2 Diet Diary

FOR NOTES



Queen Margaret University
EDINBURGH

FOOD DIARY

Improving body composition, strength, function and health related quality of life in older individuals with sarcopenic obesity through lifestyle modifications

Participant Number : _____

As part of the study you have agreed to participate in you must keep a food diary for 3 days. It is important that the information you record is as accurate as possible. The food diary should be kept for 3 complete days starting on the first day of the study.

Guidance

- Start each day on a new page
- Record the day, date and time
- Attach extra sheets to the back if required

HELPFUL HINTS FOR COMPLETING YOUR FOOD DIARY

- Record *everything* that you eat and drink
- Record what you eat and drink as close as possible to the time you consume it
- Be as accurate as possible when describing the foods you have eaten
- Think of each meal in terms of individual food items
For example,
A sandwich may consist of bread, spread, cheese & tomato
A cup of coffee may also contain milk and sugar
- Provide brand names whenever possible
- State whether foods are homemade or readymade. If you eat at the lunch club state the location and the description of the food. E.g. Brunton court: 1 portion of mashed potatoes with beans and chicken.
- Include cooking methods used. E.g. grilling, frying, boiling

PORTION SIZES

- Where possible record the actual weight of the food eaten
- Measure vegetables in terms of tablespoons/cups/bowls
- For small fruit such as grapes/ dried fruit, estimate in terms of a cup or handful
- Measure cooked rice, pasta and noodles in terms of tablespoons/cups
- Soups, salads and cereals can be estimated as a small, medium or large bowl
- State the number of slices, the type of bread and whether thin, medium or thick slices are eaten
- Fluids can be estimated as a small medium or large glass unless the specific volume is known

AN EXAMPLE OF A DAILY FOOD DIARY ENTRY

Date: 10/07/07

TIME (AM/PM)	FOOD DESCRIPTION	PORTION SIZE/ QUANTITY
7.30 am	Kellogg's Cornflakes with semi skimmed milk Toasted white bread Flora margarine Banana Fresh Orange Juice	Medium bowl 1 thick slice Thinly spread on toast 1 medium size 1 small glass
10.15 am	Tea with semi-skimmed milk and sugar Muller Light Yoghurt—Vanilla flavour	1 Mug 2 teaspoons of sugar 200 g
12.30 pm	Heinz tomato soup Sandwich (ready-made, bought in supermarket)- Wholemeal bread Margarine Spread Tuna Mayonnaise Cucumber Walkers Lite Crisps—Ready Salted Diet Coca Cola	220g tin 2 slices Thinly spread 4 slices 28 grams 1 can (330ml)
3.30 pm	Tea with semi-skimmed milk and sugar Sainsbury's digestive biscuits	2 Mugs Each mug with 2 teaspoons of sugar 2 biscuits
7.00 pm	Grilled chicken breast in breadcrumbs Boiled Potatoes Broccoli Sweet corn Apple (Golden Delicious)	Medium sized 3 egg-sized 2 tablespoons 1 tablespoon 1 medium
10.00 pm	Red Wine	2 Large-sized glasses

Date: _____

TIME (AM/PM)	FOOD DESCRIPTION	PORTION SIZE/ QUANTITY

Appendix 4.3 Formulas for the estimation of Resting Energy Expenditure

(Henry 2005)

Table IV-I Oxford predictive equations for basal metabolic rate in older adults (adopted by Henry 2005)

Sex	Age (yr)	Kcal · day ⁻¹
Men	60 – 70	13.0 bw + 567
	70+	13.0 bw + 481
Women	60 – 70	13.0 bw + 572
	70+	13.0 bw + 577

Bw, bodyweight in kg

- Example:

Female, age 73, Weight 76.0, PAL: 1.4

BMR: $10.0 \cdot W + 577 = 10.0 \cdot 76.0 + 577 = 1337$ kcal

Daily energy requirement: $1337 \cdot 1.4 = \mathbf{1872}$ kcal

Revised Energy Intake: $1872 - 500 = \mathbf{1372}$ kcal

- Daily Macronutrient Requirements

Protein: $1.2 - 1.5 \times 76.0 = \mathbf{91 - 114}$ g protein → 365 - 456kcal (27 - 33% of total energy intake)

Fat: $0.3 \times 1372 = 412/9$ kcal = **46 g fat** (30% of total energy intake)

Carbohydrates: $504 - 595$ kcal / 3.75 kcal = **135 – 158 g carbohydrate** (37 - 43 % of total energy intake)

Appendix 4.4 Sample daily diet nutritional analysis

Table IV-II A sample of a hypocaloric high protein diet for a participant in the intervention group (based on *Nutritics database*)

Meal and Food	amount	Energy (kcal)	CHO (g)	PRO (g)	FAT (g)
<u>Breakfast</u>					
Breakfast cereal, wheat biscuits	1 biscuit	66.0	14.5	2.1	0.4
Milk, skimmed	1 mug (250ml)	85.0	12.0	8.8	0.8
Peaches, raw, flesh and skin	1 medium (~110g)	36.3	8.4	1.1	0.1
<u>Morning Snack</u>					
Apples, raw, flesh and skin	1 small (~100g)	53.0	12.1	1.1	1.6
Oatcakes	1 biscuit	42.0	6.2	0.6	0.5
Coffee, black (no sugar)	1 mug	5.2	1.0	0.1	0.1
<u>Lunch</u>					
Bread, whole meal	1 medium (~35g)	80.0	15.5	3.5	0.9
Vegetables (mixed salad e.g. peas, carrots, green beans and tomatos)	1 cup (~160g)	68.0	10.8	5.4	0.8
Olive Oil	1 tsp (~5g)	37.8		trace	4.2
Cheese, Cheddar	1 slice (~30g)	125.0	0.0	7.6	10.5
Chicken, roasted	size equal to a matchbox (~30g)	53.0		8.2	2.3
Plums, raw, flesh and skin	2 medium (~110g)	21.6	5.3	0.4	0.1
<u>Afternoon Snack</u>					
Oatcakes	1 biscuit	42.0	6.2	1.1	1.6
Tea, black	1 mug			0.3	
<u>Dinner</u>					
Bread, whole meal	1 medium slice (37g)	80.0	15.5	3.5	0.9
Vegetables (mixed salad)	1 cup (~163 g)	68.0	10.8	5.4	0.8
Olive Oil	1 tsp	37.8		trace	4.2
Cheese, Cheddar	1 medium slice (~30g)	125.0	0.0	7.6	10.5
Chicken, roasted	size equal to a matchbox (~30 g)	53.0		8.2	2.3
<u>Study Drink</u>					
Promilk 50	1 bottle	320.0	26.7	51.0	1.0
Total		1398.7	145.1	113.3	43.6
Total (% of daily energy)			~40%	~30%	~30%

Appendix 4.5 Promilk 50- Full amino acid profile

Table IV-III Amino Acid profile of Promilk50

Amino Acid Profile:

	===== Per 100 ml =====		===== Per serving =====	
			500 ml	
	=====		=====	
isoleucine	670	mg	3348	mg
leucine	1310	mg	6552	mg
lysine	910	mg	4552	mg
methionine	384	mg	1918	mg
phenylalanine	665	mg	3324	mg
threonine	625	mg	3125	mg
tryptophan	158	mg	789	mg
valine	840	mg	4199	mg
alanine	129	mg	644	mg
arginine	456	mg	2279	mg
aspartic acid	308	mg	1538	mg
cystine/cysteine	84	mg	420	mg
glutamic acid	847	mg	4233	mg
glycine	77	mg	383	mg
histidine	345	mg	1727	mg
proline	388	mg	1941	mg
serine	223	mg	1116	mg
tyrosine	702	mg	3509	mg
	=====		=====	

Appendix 4.6 Example Log sheet Participant ### (Week 1 starting 25/01/16)

	Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Day		25 Jan							14 Mar								09 May		
1 Mon	Diet																		
	VitD																		
	ProMilk																		
2 Tues	Diet																		
	VitD																		
	ProMilk																		
3 Wed	Diet																		
	VitD																		
	ProMilk																		
4 Thur	Diet																		
	VitD																		
	ProMilk																		
5 Fri	Diet																		
	VitD																		
	ProMilk																		
6 Sat	Diet																		
	VitD																		
	ProMilk																		

Appendix 4.7 Dietary advice given to participants

General guidelines

- Avoid fried (especially deep fried but also pan-fried*) foods such as fried rice/noodles or fried/battered meat – instead you can bake, boil, steam or microwave.
- Try to make your own meals instead of buying processed ready-made foods.
- In general prefer lean skinless meat, such as poultry and fish, or eggs/cheese/legumes (beans) for meat-free meals. If having port you can remove the visible fat. If you buy canned fish prefer the one in water.
- If you eat out prefer stir-fried meals and eat a salad as a starter, or greens/rice instead of fried chips.
- Avoid ready-made salad dressings based on cream/mayonnaise, or creamy-soups, instead you can use olive oil/olives (as per diet plan), vinegar, lemon juice for flavor. You can also improve the flavor by using spices, herbs, fresh ginger, zest of lemon/orange, garlic and onions (you can use as much as you like of these ingredients), in your meals, salads, soups, stews etc.
- Try to limit red meat to once a week and avoid processed meat (e.g. sausages, burgers, bacon, salami etc.).
- Try to stick to the plan and consume at least five portions of fruits and vegetables a day. Prefer fresh whole fruits over canned or dry. Apart from fresh fruit, aim to eat more non-starchy vegetables: spinach, broccoli, lettuce, green beans, tomatoes, carrots, courgettes, cucumber, mushrooms etc.
- Prefer whole-grain foods like brown rice, wholegrain bread/cereal (e.g. bran flakes) and oatcakes over white (white bread/pasta etc) or sugary foods such as cakes, sweets, cookies, croissants, chocolate, donuts, etc.
- Drink lots of water and fluids throughout the day. You have no restrictions on tea as long as it has no added sugar (if sweetness is necessary you can use low-calorie sweeteners, or have your tea with a piece of fruit as per individual plan). Avoid soft drinks and sugary/fruit juices. Read the ingredients, if it mentions sugar, glucose, fructose, any kind of syrup, or concentrated fruit juice you should better avoid it.

Programme specific guidelines

- Make sure you take any notes of deviations from your individual diet plan on the log sheet, and raise any concerns that you may have regarding the diet or any other aspect of the programme with the person responsible for the programme.
- Remember to take your Vitamin D tablets. Tick (X) the relevant box on the log sheets if you

miss a tablet (there are no strict rules on the timing of this, but for your own convenience you can take it on Monday, Wednesday, Friday).

- Make sure you take one (1) Promilk every day. On the exercise days, you are advised to take it right after the exercise and on non-exercise days before bed (e.g. one hour before bed).
- Shake well the Promilks before consumption.
- Store the Promilks in a cool and dry place under 25°C. When you open it, you can consume it within 30 mins or store in the fridge for later consumption.

* You can pan-fry if you use a minimum amount of oil (as per plan) or water.

Keep coming to the exercise class. The diet and exercise work hand in hand, therefore it is important that you try your best to follow both.

Example guidelines for participants a) with a varied schedule b) who wanted to add some alcohol to the diet, c) found it difficult to adhere to portion sizes, d) could not consume Promilk50 in one sitting.

- It is very important to consume the quantities as stated in your diet plan. If necessary you may change the timings of the meals (except for the Promilk50, see above) but make sure you have some source of protein (e.g. meat, dairy, legumes) in your main meals as per diet plan.
- You can add as much leafy greens to your lunch and dinner as you like to increase the volume of the meal.
- If you feel that the lunch and/or dinner are still not enough you can also increase the portion size of the salad/vegetables but do not add more than recommended oil or salad dressing. Try to start with the salad/vegetables before the main meal. Have snacks as stated in your individual diet plan between the main meals, and ensure you drink plenty of water/tea (or other beverages as per individual plan throughout the day).
- You can have a total of three **330 mL bottles of beer OR two 330 mL beer + one small glass of wine per week**. Make sure you drink plenty of water regularly before and after the alcoholic beverage. You can also swap the alcoholic beverage for sparkling water.

Adapted from:

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<https://www.helpguide.org/articles/healthy-eating/healthy-eating.htm>

Appendix 4.8 Exercises

Table IV-IV Exercise programme

←Regression	Exercise	Progression →
	Warm Up (10 min)	
Walk next to the wall for support	Walk Around the room	Brisk Walking
	Upper Body twist- Seated	Upper body twist- Standing
	Seated arm raises (lateral and front)	
	Seated Heel Raises	
	Seated Toe raises	
	Seated Leg march	Standing by the wall single-leg raise
	Neck Rotation	
	Leg (Hip) Extension	
	Shoulder lateral rotation (external rotation)	
Tap toes laterally (Standing hip abduction/adduction)	Leg swing- lateral	
	Standing Leg curl (knee flexion)	
	Wall press	Stand slightly further away from the wall or single-arm wall press
	Standing knee raise	Knee to opposite elbow
	Mini squat with arms front raise	With trunk rotation ('wood chop')
	Balance (5-10 min)	
	Sideways walking	Grapevine walk - Fast Sideways walking with lower centre of gravity
Heel to toe parallel walk	Heel to toe walk	heel to toe walk with neck rotation
	Walking with toe raises	
	Combination footwork, with markers on the floor (as presented by Dawes and Roosen 2012)	
	Main body - Resistance (30-35 min)	
	Core	
	Trunk rotation- with straight arms	With EBs
	Seated back extension	With EBs
	Abdominal flexion seated	With EBs
	Side bend (lateral flexion/extension)	With EBs
	Legs	
	Knee Extension	With EBs
Mini Squats (knee flexion) with hands supported on the chair	Chair Stand	Squat in front of the chair (without sitting)→ Squat w. EBs
	Lateral leg abduction	With EBs
	Leg (Hip) extension	With EBs

Calf Raises Seated	Calf Raises Seated With hands on knees	Calf Raises with EBs
	Calf Raises Standing by the wall both legs	Standing single leg
Chest		
	Chest press	With EBs
	Chest Flies	With EBs
Back		
	Seated Row	With EB
	Inverse Flies	With EB
	Lat Pull down	With EB
Arms		
	Shoulder Press	With EB
	Shoulder raises, lateral	With EB
	Bicep Curls	With EB
	Tricep Extension	With EB
<u>Cool down- Stretching (10 mins)</u>		

Stretching for: Neck, Shoulder, Triceps, Biceps, Chest, Back, Abs, Quadriceps, Hamstring, Calf

Adapted from:

BAECHLE, T.R. and WESTCOTT, 2010. *Fitness professional's guide to Strength Training Older Adults*. 2nd ed. Leeds: Human Kinetics.

DAWES, J. and ROOSEN, M., 2012. *Developing Agility and Quickness*. Leeds: Human Kinetics.

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Appendix 4.9 Sample size calculation

Sample size equation:
$$n = \frac{2[(a + b)^2 \sigma^2]}{(\mu_1 - \mu_2)^2}$$

n = sample size in each group

μ_1 = population mean in treatment Group 1

μ_2 = population mean in treatment Group 2

$\mu_1 - \mu_2$ = the difference the investigator wishes to detect

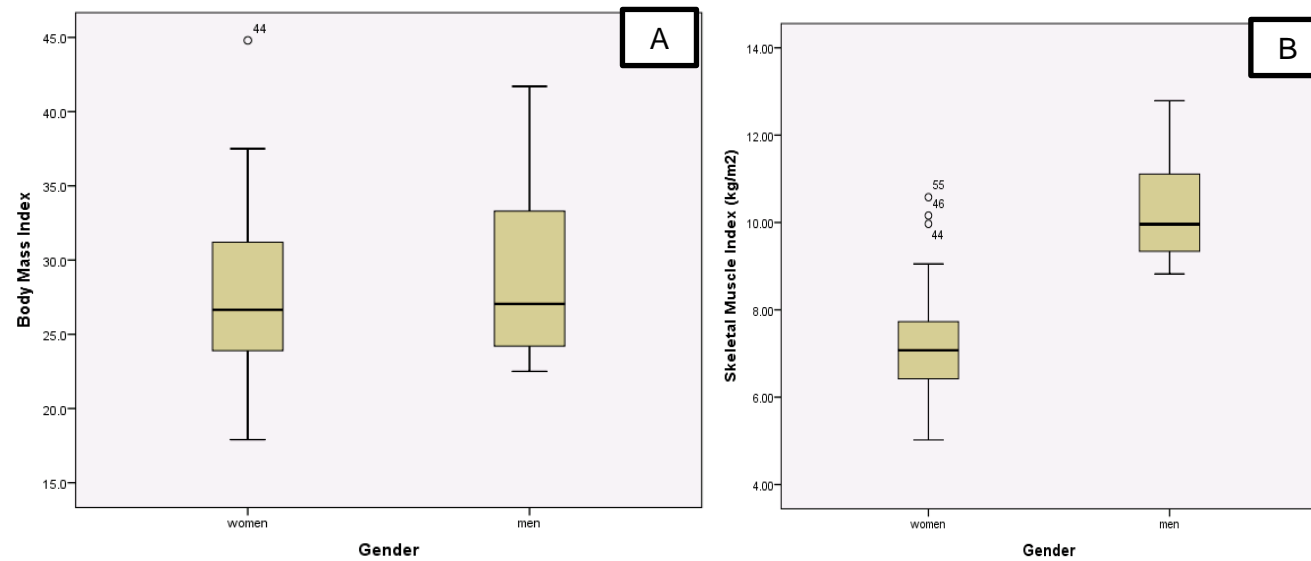
σ^2 = population variance (SD)

a = 1.96 (conventional multiplier for alpha = 0.05)

b = 0.842 (conventional multiplier for power = 0.80)

Figure IV-II. Calculation of sample size assuming alpha =0.05 and power =0.80 (Noordzij et al. 2010).

Appendix 5 Outliers in cross-sectional data



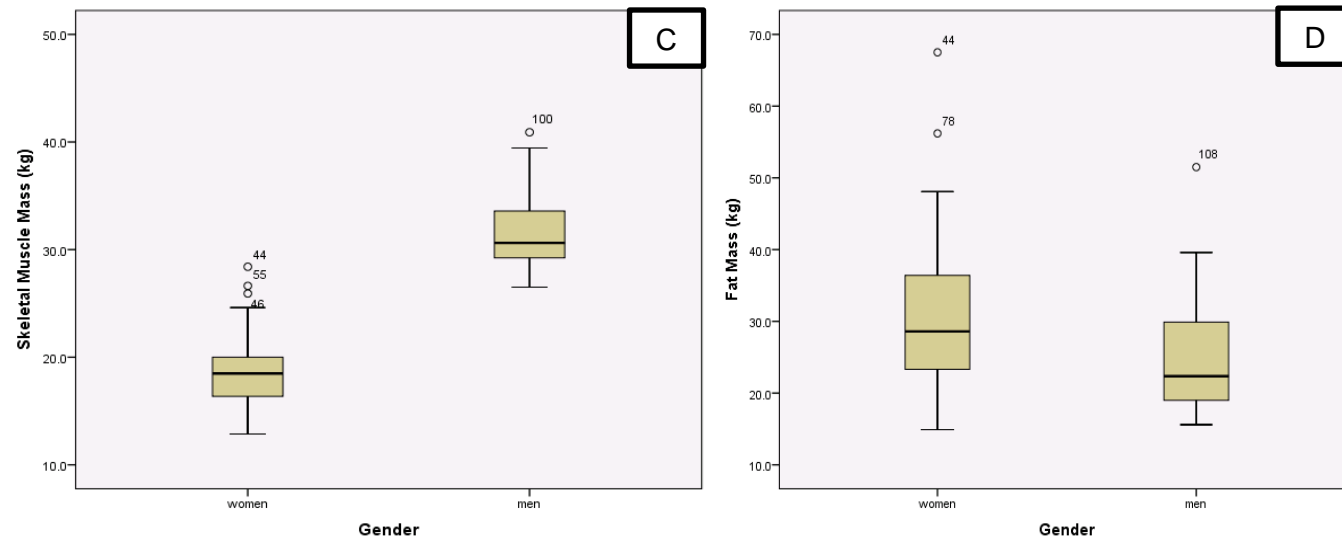


Figure V. Boxplots for BMI (A), SMI (B), SMM (C), and Fat mass (D) for the screening test (Test 1) in men (n=29) and women (n=79) of the overall cohort.

Publication 1: Systematic Review

THEODORAKOPOULOS, C., JONES, J., BANNERMAN, E. and GREIG, C., 2017.
Effectiveness of nutritional and exercise interventions to improve body composition and muscle strength or function in sarcopenic obese older adults: A systematic review. *Nutrition Research*. May, vol. 43, pp. 3-15.

Publication 2: Poster presentation

Geriatrics 1

S57

SUN-P034

HANDGRIP STRENGTH, MINI NUTRITIONAL ASSESSMENT AND SWALLOWING FINDINGS IN THE ELDERLY WITHOUT SWALLOWING COMPLAINTS

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Rationale: Primary sarcopenia has been considered an independent risk factor in dysphagia in elderly individuals; thus, the objective of the study was to evaluate the strength of handgrip, conduct nutritional screening and assess swallowing in the elderly without swallowing complaints.

Methods: The study is prospective, descriptive; included elderly individuals 60-79 years without swallowing complaints while excluding those with neurological disorders, cognitive deficits and/or head and neck sequela. Nutritional risk evaluation was carried out through mini nutritional assessment (MNA), assessment of handgrip strength through isokinetic dynamometer and assessment of swallowing by videofluoroscopy, which included thin, nectar-thick, honey-thick, pudding-thick, soft solid and dry solid consistencies.

Results: We evaluated 15 elderly individuals (12 male, 3 female) with a mean age of 69.26 years. As for MNA values, 13.3% of the elderly showed risk of malnutrition and 1 individual (6.6%) was considered malnourished. The mean hand grip strength found was 29.53 kg/f for the right and 25.5 kg/f for the left. Swallowing deficits found included: chewing (20%), reduction of oral ejection force (33.3%), posterior escape (100%), and residue found after swallowing in the tongue region (40%), vallecula (53.3%), pyriform sinus (6.6%) and pharynx (26.6%). In relation to aspiration risk, 13.3% had penetration (entry of food to the vocal fold region) with liquid consistency. Regarding the esophageal phase, 13.3% of the elderly showed tertiary waves and delayed gastric emptying.

Conclusion: Dysphagia in the elderly with risk of aspiration may be related to primary sarcopenia. The study continues this line of research with a control group of another age group to perform correlations.

Disclosure of Interest: None declared

SUN-P035

SCREENING FOR SARCOPENIA AND SARCOPENIC OBESITY IN SCOTTISH COMMUNITY-DWELLERS >65 YEARS

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Rationale: Sarcopenia, obesity and sarcopenic obesity (SO) are recognised as major public health concerns affecting older adults' health and quality of life, however identifying and managing these conditions can be challenging due to a plethora of different definition criteria [1], [2]. This study aimed to screen for sarcopenia, obesity and SO, in independent-living older Scottish adults using two different criteria.

Methods: Dual frequency bioelectrical impedance analysis was used to estimate body composition, hand grip dynamometry to measure strength. Sarcopenia was defined: skeletal muscle index <6.76 kg*m⁻² (f) and <10.76 kg*m⁻² (m) and handgrip strength <20 kg (f) and <30 kg (m) [1]; Obesity a) BMI > 30 kg*m⁻² or b) percent body fat >40% (f) and >28% (m) [3]. **Results:** One hundred and eight people, median (IQR) age 70 (67, 75) years and BMI 26.9 (24.0, 31.0) kg*m⁻² participated. Sixty-three percent (raised %BF) vs 27.8% (BMI > 3 g*m⁻²) were classed as obese; 12% were SO (%BF) vs 4.6% SO (BMI > 30 kg*m⁻²) (Table 1).

Table 1: Sarcopenia, Obesity and Sarcopenic Obesity in Scottish older adults

	Men n = 29 (%)	Women n = 79 (%)	All n = 108 (%)
Sarcopenic	4 (13.8)	12 (15.2)	16 (14.8)
Obese (%BF)	12 (41.4)	56 (70.9)	67 (63.0)
Obese (BMI)	2 (24.1)	23 (29.1)	29 (27.8)
SO (%BF)	2 (6.9)	11 (13.9)	13 (12.0)
SO (BMI)	0 (0)	5 (6.3)	5 (4.6)

Conclusion: BMI underestimates body fat in older adults and thus underestimates SO. Sarcopenia and SO may be higher in Scottish adults >65 y than other UK studies (sarcopenia 4.6-0.9%) [4] and European countries (SO 0-2.3%) [5].

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- [1] Cruz-Jentoft AJ, Baeyens JP, Bauer JM et al. (2010) *Age Ageing*, 39 (4), 412-23.
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Disclosure of Interest: None declared

SUN-P036

NUTRITIONAL STATUS AND HEALTH-RELATED QUALITY OF LIFE IN ACUTE GERIATRIC PATIENTS

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Rationale: Malnutrition is a frequent phenomenon observed in elderly patients. Some studies suggest that nutritional status affects health-related quality of life (HRQoL). This relationship has not been thoroughly examined in acute geriatric (AG) patients. The aim of this study was therefore to investigate the associations between nutritional status and HRQoL in a group of AG patients.

Methods: One hundred and twenty patients >65 years admitted to the AG ward of two different hospitals were included in this cross-sectional study. Mini Nutritional Assessment (MNA) was used to measure nutritional status, MNA scores <17 indicated malnutrition and 17-23.5 risk of malnutrition. HRQoL was assessed using Short Form 36, version 2(SF-36v2). A multiple

Publication 3: Oral Poster Presentation

Poster Tour 2: Geriatrics

S23

Results: Nitrogen balance (ΔN) was lower ($p < 0.05$) in all models of injury compared to basal and to controls from D1 to D3. In addition ΔN was worse in LPS-Cit.

ΔN (g/24 h)	D0	D1	D2	D3
C	0.56 \pm 0.07	0.57 \pm 0.06	0.60 \pm 0.06	0.54 \pm 0.14
LPS-NEAA	0.49 \pm 0.09	-0.33 \pm 0.06a	0.21 \pm 0.12ab	0.17 \pm 0.16ab
LPS-Cit	0.49 \pm 0.07	-0.29 \pm 0.08a	0.10 \pm 0.04a	0.04 \pm 0.12a

a: $p < 0.001$ vs control b: $p < 0.05$ vs LPS-NEAA vs LPS-Cit. MPS was similar in catabolic and CI groups in the Soleus but significantly higher in EDL in LPS-Cit (LPS-Cit: 4.5 ± 1.7 vs C: 2.3 ± 1.2 ; $p < 0.001$ and vs LPS-NEAA: 3.1 ± 2.3 $p < 0.05$). S6K1 phosphorylation in the EDL was also higher in LPS-Cit vs C (C: 0.42 ± 0.28 LPS-Cit: 0.94 ± 0.51 $p < 0.05$).

Conclusion: Cit effect differs according to the type of injury and the muscle studied. The deteriorated ΔN despite higher MPS rate and mTOR activation suggests elevated protein degradation and very limited effect of Cit in critical illness.

Disclosure of Interest: O. Kuci: None declared, D. Verlaan: None declared, C. Vicente: None declared, E. Nubret: None declared, S. Le Plénier Shareholder of: Citrage, J.-P. De Bandt Shareholder of: Citrage, L. Cynober Shareholder of: Citrage

PT01.6

MALNUTRITION PREDICTS IN-HOSPITAL MORTALITY IN PATIENTS WITH ASPIRATION PNEUMONIA

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Rationale: Aspiration pneumonia (AP) occurs in older adults with impaired swallowing function, which causes malnutrition. Although malnutrition increases the risk for AP, whether malnutrition is associated with the outcomes of AP remains unclear. This study aimed to determine the association between nutritional status and mortality due to AP.

Methods: This prospective cohort study included 353 consecutive AP patients aged >64 years admitted to our geriatric hospital between June 2013 and August 2015. Age, sex, nutritional status assessed using the Mini Nutritional Assessment-Short Form (MNA-SF), pneumonia severity assessed using the Japanese version of CURB-65, Barthel index (BI), Charlson comorbidity index, and C-reactive protein (CRP) level were evaluated for their associations with 30-day and in-hospital mortality.

Results: The mean age of the patients (50.4% men) was 85.6 ± 7.8 years, and the median MNA-SF score was 7 (6-9). Mild, moderate, severe, and extremely severe pneumonia were observed in 2.0%, 73.1%, 22.4%, and 2.5% of patients, respectively. Patients with 30-day mortality had more severe pneumonia ($p = 0.001$), higher CRP levels (11.2 ± 9.1 vs 8.9 ± 6.7 mg/dL, $p = 0.044$), and lower BI (0 [0-15] vs 20 [0-60], $p < 0.001$) than the survivors. Patients with in-hospital mortality also had more severe pneumonia ($p = 0.001$), higher CRP levels (13.9 ± 10.0 vs 8.9 ± 6.7 mg/dL, $p = 0.001$), and lower BI (5 [0-17.5] vs 15 [0-55], $p = 0.029$). Although univariate analyses did not show a statistical difference, in the multivariate analysis, MNA-SF was independently associated with in-hospital mortality after adjusting for pneumonia severity, age, and sex (adjusted OR = 0.876, $p = 0.029$).

Conclusion: Malnutrition upon admission in AP patients is associated with in-hospital mortality. Premorbid and in-hospital nutritional care might be essential for recovery from AP.

Disclosure of Interest: None declared

Poster Tour 2: Geriatrics

PT02.1

DO DIFFERENT OBESITY-CRITERIA RESULT IN DIFFERENT PHENOTYPES IN OLDER PEOPLE?

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Rationale: Sarcopenic obesity is a public health concern but identification of obesity in older age is challenging.¹ The aim of this study was to identify and compare obesity phenotypes using two different criteria.

Methods: In a sample of Scottish community dwellers aged ≥ 65 y, body composition (assessed using dual Bioelectrical Impedance Analysis) and strength (measured using handgrip dynamometry) were compared, defining obesity as (a) Body Mass Index (BMI) >30 kg/m² or (b) %body fat (%BF) >28 (m) and >40 (f).² A Mann-Whitney test was used to detect differences in obese vs non-obese phenotypes.

Results: 108 participants, median (IQR) age 70 (67, 75)y, were screened. Based on BMI classification, obese adults had a significantly higher skeletal muscle mass (SMM) than the non-obese, however strength was not different between the groups (Table 1). Based on %BF the opposite pattern was observed; the non-obese adults had higher SMM and were also stronger than the obese. %BF identified more cases of obesity.

Table 1: Characteristics of obese vs non-obese older adults

	BMI		%BF	
	Non-Obese N = 78	Obese N = 30	Non-Obese N = 40	Obese N = 68
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
BMI (kg/m ²)	25.5 (23.3-27.1)	34.7 (32.7-36.8)**	23.9 (22.6-26.6)	29.2 (25.9-34.5)**
%BF	38.4 (28.8-42.3)	47.3 (40.0-50.3)**	33.9 (26.1-37.9)	43.7 (40.8-48.8)**
Fat Mass (kg)	24.0 (20.9-28.3)	40.0 (35.7-47.3)**	21.4 (19.1-22.8)	32.5 (28.0-39.6)**
SMM (kg)	18.7 (16.4-26.7)	21.8 (19.1-28.4)*	21.1 (18.7-16.4)*	18.9 (16.4-21.8)
Strength (kg)	25.0 (21.5-31.8)	25.5 (21.5-30.5)	27.5 (24.5-42.3)**	24.5 (20.0-28.0)

Significance * $p < 0.01$, ** $p < 0.001$

Conclusion: Classification of the older obese phenotype is dependent upon method of assessment. A consensus for the definition criteria of obesity in older age is crucial in order to identify obesity and sarcopenic obesity.

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- Prado CMM, Wells JCK, Smith SR et al. (2012) *Clinical Nutrition*, 31 (5), 583-601.
- Baumgartner RN, Wayne SJ, Waters DL et al. (2004) *Obes Res*, 12 (12), 1995-2004.

Disclosure of Interest: None declared

Publication 4: Oral Presentation

Screening for sarcopenia and dynapenia in older Scottish community-dwellers; the impact of body composition on muscle strength and quality.

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Keywords: Dynapenia, Sarcopenia, Muscle Strength, Muscle Quality

Background: Dynapenia (loss of muscle strength) and sarcopenia (the combined loss of muscle mass and strength/function) are both associated with physical disabilities in older adults^{[1][2]}. Moreover, fat mass may impact the development/progression of these conditions as high adiposity has been associated with lower muscle quality and higher rates of lean mass losses^[3].

Objectives: This study examined the relationship between body composition and muscle strength and quality in older Scottish community-dwellers screened for sarcopenia and dynapenia.

Methods: The European Working Group on Sarcopenia in Older People (EWGSOP) criteria were used^[2]: low strength (dynapenia) was defined as handgrip strength (HG) <20kg in women and <30kg in men and sarcopenia as skeletal muscle index <6.76 kg*m⁻² in women and <10.76 kg*m⁻² in men, combined with dynapenia. Dual frequency bioelectrical impedance analysis (BIA) was used to estimate fat mass (kg) lean mass (kg) and skeletal muscle mass (SMM; kg) and a handgrip dynamometer to measure HG. Muscle quality was defined as the ratio of HG per unit of lean mass. A Spearman's test was used to assess associations between handgrip, muscle quality and body composition.

Results: One hundred and eight people were screened (29m, 79f), median (IQR) age 70 (67, 75) years and BMI 26.9 (24.1, 30.7) kg*m⁻². Prevalence of dynapenia was 17.2% in men and 21.5% in women and sarcopenia 13.8% in men and 15.2% in women. Handgrip strength was significantly associated with both lean mass (n=105; rho=0.62, p<0.001) and SMM (rho=0.63, p<0.001), whereas a small but significant negative relationship was observed between handgrip strength and fat mass (rho=-0.25, p<0.01). Muscle quality was significantly and negatively associated with fat mass (n=105; rho=-0.51 p<0.001) (Figure 1).

